

10523015.trn

*Intore*

AUTHOR(S): Kim, Hui Hyun; Ji, Hye Young; Lee, Hye Won; Kim, Soon Ai; Lee, Seonkyoung Yi, Kyu Yang; Lee, Hye Suk

CORPORATE SOURCE: Drug Metabolism and Bioanalysis Laboratory, College of Pharmacy and Medicinal Resources Research Institute, Wonkwang University, Iksan, S. Korea

SOURCE: Drug Development Research (2006), Volume Date 2005, 66(1), 40-49

CODEN: DDREDK; ISSN: 0272-4391

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The in vitro metabolism and the transport of a novel anti-angiogenic agent KR-31831, (2R,3R,4S)-6-amino-4-[N-(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)amino]-3-hydroxy-2-dimethoxymethyl-3,4-dihydro-2-methyl-2H-1-benzopyran were investigated. Liquid chromatog.-mass spectrometry and tandem mass spectrometry were used for qual. and quant. anal. The bidirectional transport studies of KR-31831 using Caco-2 cell monolayers showed the efflux to be significantly higher than influx ( $29.1 \pm 10^{-6}$  compared to  $11.5 \pm 10^{-6}$  cm/s). P-glycoprotein inhibitors significantly increased the influx of KR-31831 and decreased the efflux of KR-31831. These data indicate that KR-31831 is a substrate for an efflux pump, P-glycoprotein. The incubations of KR-31831 with human liver microsomes produced three metabolites, M1, M2, and M3. M1 and M2 were identified as N-(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)amine and (2R,3R,4S)-6-amino-4-N-(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)aminol-3-hydroxy-2-hydroxymethyl-3,4-dihydro-2-methyl-2H-1-benzopyran by comparison with the authentic stds. M3 was tentatively characterized as hydroxy-KR-31831. CYP3A4 was identified as the major enzyme responsible for KR-31831 metabolism to a major metabolite M1 using the combination of correlation anal., immuno-inhibition, chemical inhibition in human liver microsomes, and metabolism by cDNA expressed CYP enzymes. There is the possibility of drug-drug interactions when prescribing KR-31831 concomitantly with known inhibitors or inducers of CYP3A4 and P-glycoprotein. KR-31831 was found to inhibit potently the metabolism of CYP2D6 substrate, suggesting that coadministration of KR-31831 with CYP2D6 substrates may have significant effects on the pharmacokinetics of CYP2D6 substrates.

IT 571141-49-6, KR-31831  
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(characterization of cytochrome P 450 enzymes and P-glycoprotein involved in metabolism and transport of a new anti-angiogenic agent KR-31831)

RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-  
(CA INDEX NAME)

Absolute stereochemistry.

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NEWS 3 JAN 16 CA/CAPLUS Company Name Thesaurus enhanced and reloaded  
NEWS 4 JAN 16 IPC version 2007.01 thesaurus available on STN  
NEWS 5 JAN 16 WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data  
NEWS 6 JAN 22 CA/CAPLUS updated with revised CAS roles  
NEWS 7 JAN 22 CA/CAPLUS enhanced with patent applications from India  
NEWS 8 JAN 29 PHAR reloaded with new search and display fields  
NEWS 9 JAN 29 CAS Registry Number crossover limit increased to 300,000 in  
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NEWS 11 FEB 15 RUSSIAPAT enhanced with pre-1994 records  
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NEWS 13 FEB 26 MEDLINE reloaded with enhancements  
NEWS 14 FEB 26 EMBASE enhanced with Clinical Trial Number field  
NEWS 15 FEB 26 TOXCENTER enhanced with reloaded MEDLINE  
NEWS 16 FEB 26 IFICDB/IFIPAT/IFIUDB reloaded with enhancements  
NEWS 17 FEB 26 CAS Registry Number crossover limit increased from 10,000  
to 300,000 in multiple databases  
NEWS 18 MAR 15 WPIDS/WPIX enhanced with new FRAGHITSTR display format  
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NEWS 21 MAR 22 LWPI reloaded  
NEWS 22 MAR 30 RDISCLOSURE reloaded with enhancements  
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AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.  
  
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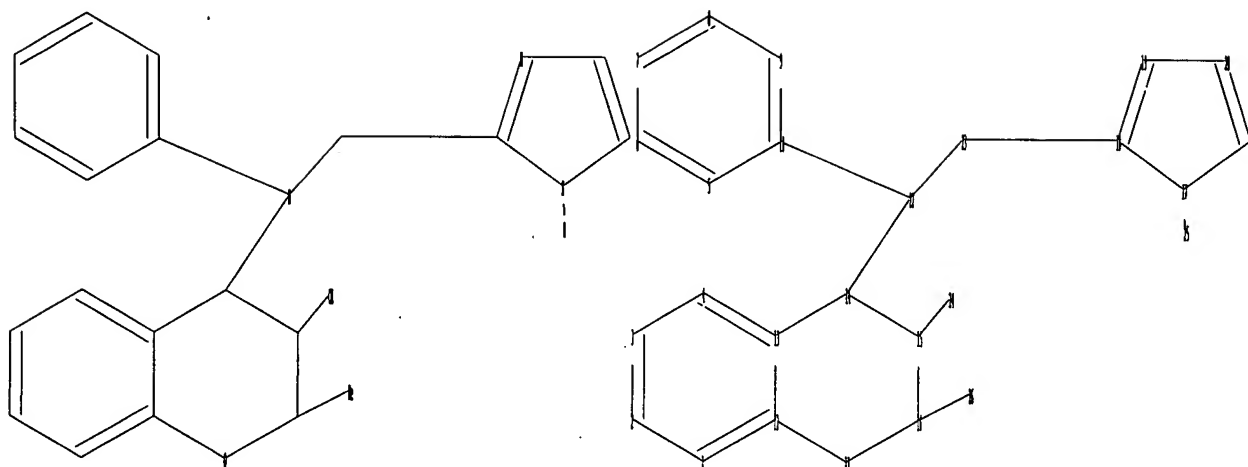
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chain nodes :
22 23 24 25 26
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
chain bonds :
10-22 14-22 15-24 16-26 17-25 18-23 22-23
ring bonds :
1-2 1-12 2-3 3-4 4-13 5-6 5-10 6-7 7-8 8-9 9-10 11-12 11-16 12-13
13-14 14-15 15-16 17-18 17-21 18-19 19-20 20-21
exact/norm bonds :
10-22 14-22 15-24 17-18 17-21 18-19 19-20 22-23
exact bonds :
11-12 11-16 13-14 14-15 15-16 16-26 17-25 18-23 20-21
normalized bonds :
1-2 1-12 2-3 3-4 4-13 5-6 5-10 6-7 7-8 8-9 9-10 12-13
isolated ring systems :
containing 1 : 5 : 17 :

```

```

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS

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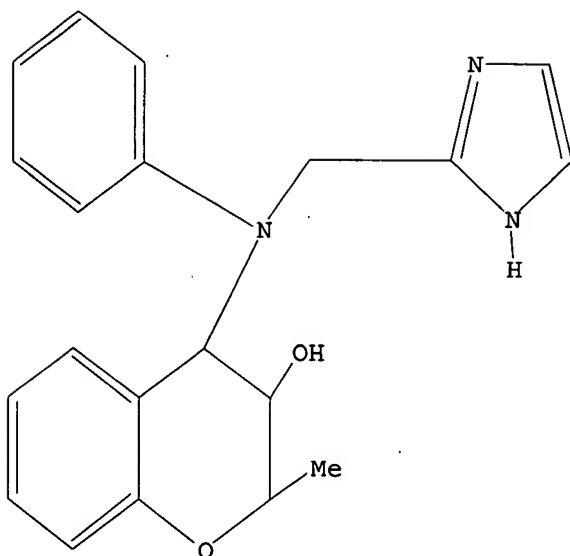
L1 STRUCTURE UPLOADED

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=> d l1
L1 HAS NO ANSWERS
L1 STR

```

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Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 14:33:53 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 11 TO ITERATE

100.0% PROCESSED 11 ITERATIONS

4 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*

BATCH \*\*COMPLETE\*\*

PROJECTED ITERATIONS: 22 TO 418

PROJECTED ANSWERS: 4 TO 200

L2 4 SEA SSS SAM L1

=> s l1 sss full

FULL SEARCH INITIATED 14:33:59 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 259 TO ITERATE

100.0% PROCESSED 259 ITERATIONS

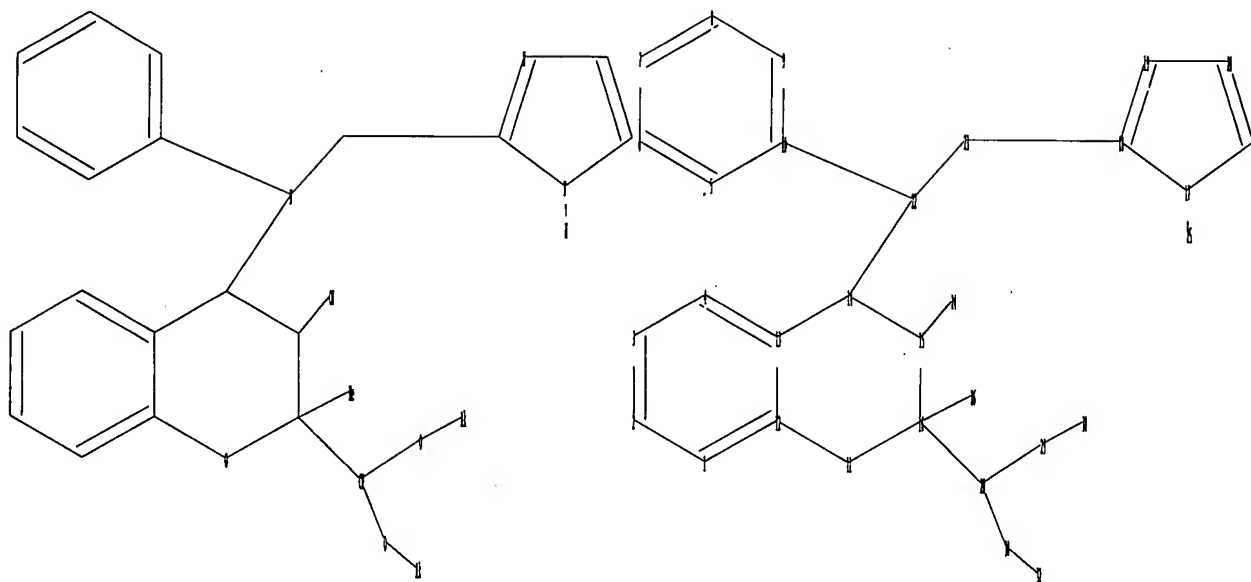
SEARCH TIME: 00.00.01

L3 71 SEA SSS FUL L1

=>

Uploading C:\Program Files\Stnexp\Queries\10523015a.str

71 ANSWERS



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chain nodes :
22 23 24 25 26 28 29 30 31 32
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
chain bonds :
10-22 14-22 15-24 16-26 16-28 17-25 18-23 22-23 28-29 28-30 29-31 30-32
ring bonds :
1-2 1-12 2-3 3-4 4-13 5-6 5-10 6-7 7-8 8-9 9-10 11-12 11-16 12-13
13-14 14-15 15-16 17-18 17-21 18-19 19-20 20-21
exact/norm bonds :
10-22 14-22 15-24 17-18 17-21 18-19 19-20 22-23 28-29 28-30 29-31 30-32
exact bonds :
11-12 11-16 13-14 14-15 15-16 16-26 16-28 17-25 18-23 20-21
normalized bonds :
1-2 1-12 2-3 3-4 4-13 5-6 5-10 6-7 7-8 8-9 9-10 12-13
isolated ring systems :
containing 1 : 5 : 17 :

```

Match level :

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1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 28:CLASS
29:CLASS 30:CLASS 31:CLASS 32:CLASS

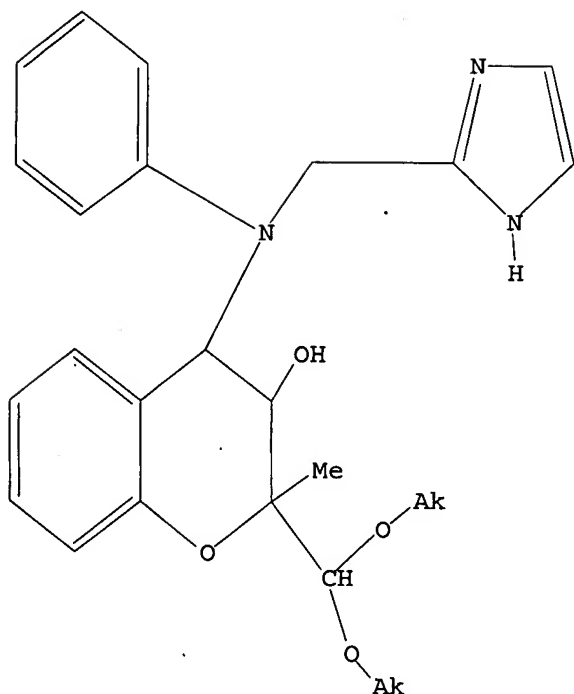
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L4 STRUCTURE UPLOADED

=> d 14

L4 HAS NO ANSWERS

L4 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 14

SAMPLE SEARCH INITIATED 14:36:51 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 7 TO ITERATE

100.0% PROCESSED 7 ITERATIONS

4 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*

BATCH \*\*COMPLETE\*\*

PROJECTED ITERATIONS: 7 TO 298

PROJECTED ANSWERS: 4 TO 200

L5 4 SEA SSS SAM L4

=> s 14 sss full

FULL SEARCH INITIATED 14:36:58 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 166 TO ITERATE

100.0% PROCESSED 166 ITERATIONS

SEARCH TIME: 00.00.01

52 ANSWERS

L6 52 SEA SSS FUL L4

=> FIL HCAPLUS

COST IN U.S. DOLLARS

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ENTRY

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L1	STRUCTURE UPLOADED
L2	4 S L1
L3	71 S L1 SSS FULL
L4	STRUCTURE UPLOADED
L5	4 S L4
L6	52 S L4 SSS FULL

FILE 'HCAPLUS' ENTERED AT 14:37:03 ON 20 APR 2007

=> s l3

L7 32 L3

=> s l6

L8 8 L6

=> s l7 and py<=2002

22870547 PY<=2002

L9 12 L7 AND PY<=2002

=> s l8 and py<=2002

22870547 PY<=2002

L10 0 L8 AND PY<=2002

=> d l8 ibib abs hitstr tot

L8 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:1199201 HCAPLUS

DOCUMENT NUMBER: 146:19691

TITLE: KR-31831, a new synthetic anti-ischemic agent, inhibits in vivo and in vitro angiogenesis

AUTHOR(S): Yi, Eui-Yeun; Park, Shi-Young; Song, Hyun Seok; Son, Myung Jin; Yi, Kyu-Yang; Yoo, Sung-En; Kim, Yung-Jin



CORPORATE SOURCE: Department of Molecular Biology, Pusan National University, Pusan, 609-735, S. Korea  
SOURCE: Experimental and Molecular Medicine (2006), 38(5), 502-508  
CODEN: EMMEF3; ISSN: 1226-3613  
PUBLISHER: Korean Society of Medical Biochemistry and Molecular Biology  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Angiogenesis is considered to be an integral process to the growth and spread of solid tumors. Anti-angiogenesis therapy recently was found to be 1 of the most promising anti-cancer therapeutic strategies. In this study, we provide several lines of evidences showing that KR-31831, a new benzopyran derivative, has anti-angiogenic activities. KR-31831 inhibited the proliferation, migration, invasion and tube formation of bovine aortic endothelial cells (BAECs), and suppressed the release of matrix metalloproteinase-2 (MMP-2) of BAECs. KR-31831 also inhibited in vivo angiogenesis in mouse Matrigel plug assay. Furthermore, the mRNA expressions of basic fibroblast growth factor (bFGF), fibroblast growth factor receptor-2 (FGFR-2), and vascular endothelial growth factor receptor-2 (VEGFR-2) were decreased by KR-31831. Taken together, these results suggest that KR-31831 acts as a novel angiogenesis inhibitor and might be useful for treating hypervascularized cancers.

IT 571141-49-6, KR-31831

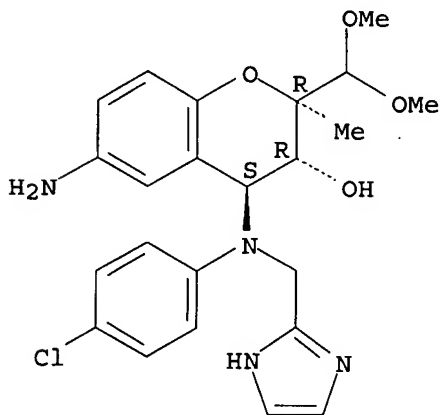
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(KR-31831 inhibits in vivo and in vitro angiogenesis)

RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S) - (CA INDEX NAME)

Absolute stereochemistry.



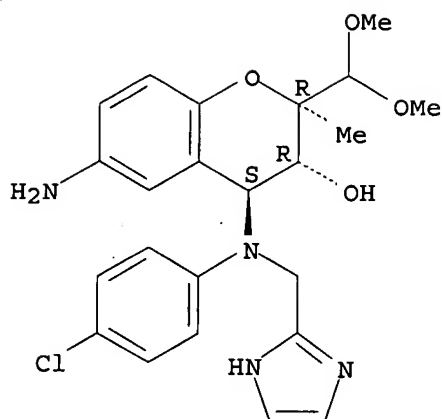
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L8 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:146422 HCAPLUS

DOCUMENT NUMBER: 144:183984

TITLE: Characterization of cytochrome P450 enzymes and P-glycoprotein involved in the metabolism and transport of a new anti-angiogenic agent KR-31831



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:1082825 HCAPLUS

DOCUMENT NUMBER: 143:452120

TITLE: Metabolism of a novel antiangiogenic agent KR-31831 in rats using liquid chromatography-electrospray mass spectrometry

AUTHOR(S): Kim, Hui-Hyun; Paek, In-Bok; Ji, Hye Young; Lee, Sunkyung; Yi, Kyu Yang; Lee, Hye Suk

CORPORATE SOURCE: Drug Metabolism and Bioanalysis Laboratory, College of Pharmacy and Phytofermentation Research Center, Wonkwang University, Iksan, S. Korea

SOURCE: Journal of Separation Science (2005), 28(14), 1818-1822

PUBLISHER: CODEN: JSSCCJ; ISSN: 1615-9306 Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

AB KR-31831 ((2S,3R,4S)-4-(((1H-imidazol-2-yl)methyl)(4-chlorophenyl)amino)-6-amino-2-(dimethoxymethyl)-2-methyl-3,4-dihydro-2H-chromen-3-ol) is a novel antiangiogenic agent. In vitro and in vivo metabolism of KR-31831 in rats has been investigated using LC-MS and LC-MS/MS anal. Incubation of rat liver microsomes and hepatocytes with KR-31831 produced three metabolites (M1-M3). M1, M2, and M3 were identified as N-((1H-imidazol-2-yl)methyl)-4-chlorobenzenamine, (2R,3R,4S)-4-(((1H-imidazol-2-yl)methyl)(4-chlorophenyl)amino)-6-amino-2-(hydroxymethyl)-2-methyl-3,4-dihydro-2H-chromen-3-ol, and N-((2S,3R,4S)-4-(((1H-imidazol-2-yl)methyl)(4-chlorophenyl)amino)-2-(dimethoxymethyl)-3-hydroxy-2-methyl-3,4-dihydro-2H-chromen-6-yl)acetamide, resp., by co-chromatog. with the authentic stds. and by comparison with product ion spectra of the authentic stds. Those in vitro metabolites were also detected in bile, plasma, or urine samples after an i.v. administration of KR-31831 to rats. The metabolic routes for KR-31831 included the metabolism of acetal group to hydroxymethyl group (M2), N-dealkylation to M1, and N-acetylation at the 6-amino group (M3).

IT 869116-59-6

RL: ANT (Analyte); ANST (Analytical study)

(metabolism of a novel antiangiogenic agent KR-31831 in rats using liquid chromatog.-electrospray mass spectrometry)

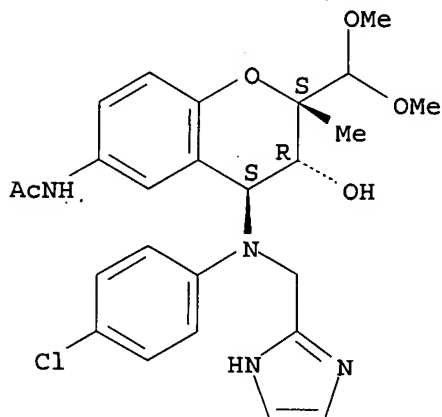
RN 869116-59-6 HCAPLUS

CN Acetamide, N-[(2S,3R,4S)-4-[(4-chlorophenyl)(1H-imidazol-2-yl)methyl]amino]-

10523015.trn

2-(dimethoxymethyl)-3,4-dihydro-3-hydroxy-2-methyl-2H-1-benzopyran-6-yl]-  
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 571141-49-6, KR 31831

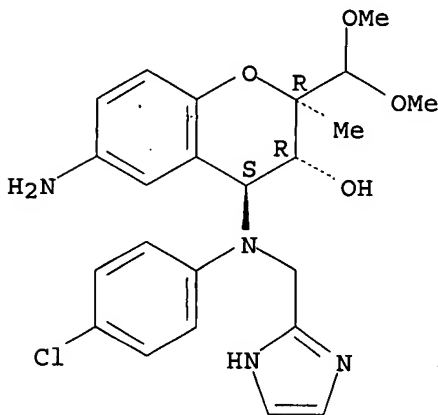
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL  
(Biological study)

(metabolism of a novel antiangiogenic agent KR-31831 in rats using liquid  
chromatog.-electrospray mass spectrometry)

RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-  
ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-  
(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

7

THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:452927 HCAPLUS

DOCUMENT NUMBER: 144:232975

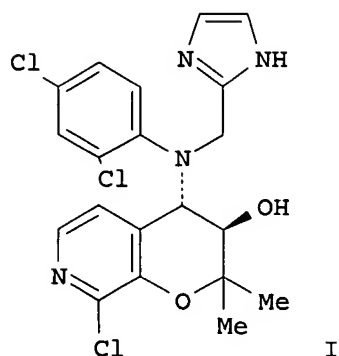
TITLE: 4-[(N-imidazol-2-ylmethyl)anilino]pyranopyridine  
analogs as novel anti-angiogenic agents

AUTHOR(S): Lee, Sunkyung; Chae, Sun Mi; Yi, Kyu Yang; Kim,

04/20/2007

Page 11

CORPORATE SOURCE: Nakjeong; Oh, Chang Ho  
 Medicinal Science Division, Korea Research Institute  
 of Chemical Technology, Daejeon, 305-600, S. Korea  
 SOURCE: Bulletin of the Korean Chemical Society (2005), 26(4),  
 619-628  
 CODEN: BKCSDE; ISSN: 0253-2964  
 PUBLISHER: Korean Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 OTHER SOURCE(S): CASREACT 144:232975  
 GI



AB Replacement of the benzopyran ring with pyranopyridines was accomplished for 4-[(N-imidazol-2-ylmethyl)-4-chloroanilino]benzopyran, previously discovered as anti-angiogenic agent with antitumor activity. The [3,2-c]-, [3,2-b]-, [2,3-c]-, and [2,3-b]-pyranopyridines with N-(imidazol-2-ylmethyl)aniline moiety at the 4-position (e. g. I), were synthesized, and evaluated for primary anti-angiogenic properties through primary cultured HUVEC tube formation assay. The pyranopyridine ring, especially [3,2-b]- and [2,3-c]-isomer, can replace the benzopyran ring and can be optimized through the introduction of substituents both on the pyranopyridine ring and the aniline moiety for the identification of a novel anti-angiogenic agent.

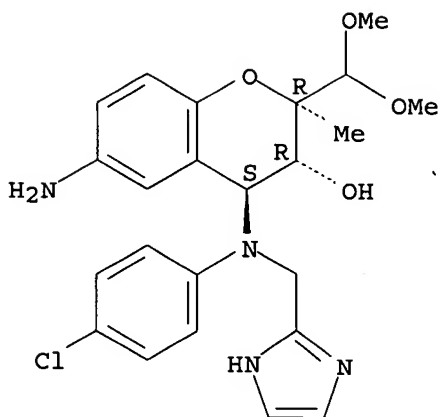
IT 571141-49-6

RL: PAC (Pharmacological activity); BIOL (Biological study)  
 (preparation and angiogenesis inhibition by [(N-imidazolylmethyl)anilino]pyranopyridine isomers prepared via pyranopyridine epoxidn. followed by ring opening reactions with (imidazolylmethyl)anilines)

RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-  
 (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:95257 HCAPLUS

DOCUMENT NUMBER: 142:309403

TITLE: Pharmacokinetics of a novel antiangiogenic agent  
KR-31831 in rats

AUTHOR(S): Kim, Sook J.; Lee, Hong I.; Ji, Hye Y.; Moon, Ya;  
Paek, In B.; Lee, Sunkyung; Yi, Kyu Y.; Yoo, Sun D.;  
Lee, Hye S.

CORPORATE SOURCE: Drug Metabolism and Bioanalysis Laboratory, College of  
Pharmacy, Wonkwang University, Iksan, 570-749, S.  
Korea

SOURCE: Biopharmaceutics & Drug Disposition (2005), 26(1),  
21-26

CODEN: BDDID8; ISSN: 0142-2782

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study reports the absorption, dose-linearity and pharmacokinetics of a novel antiangiogenic agent KR-31831 in rats after i.v. and oral administration at doses of 5, 10 and 25 mg/kg on both occasions. Concns. of KR-31831 were determined by a validated LC/MS/MS assay method. After i.v. injection, plasma concentration-time profiles showed multi-compartmental characteristics, and there were no significant differences in Cl (20.8-27.7 mL/min/kg) and dose-normalized AUC (178.1-231 µg · min/mL based on the 5 mg/kg dose) as a function of dose. However, Vss was significantly increased at the 25 mg/kg dose (4931 mL/kg) compared with those (2288-2421 mL/kg) at lower doses. Subsequently, t<sub>1/2</sub> was increased from 143-159 min at the lower doses to 304 min at the 25 mg/kg dose. The altered VSS was found to be a result of reduced plasma protein binding at relatively high concns. Following oral administration (doses 5-25 mg/kg), the absolute oral bioavailability ranged from 37.8% to 46.3%, and there were no significant alterations in dose-normalized AUC, T<sub>max</sub>, C<sub>max</sub> and t<sub>1/2</sub> as a function of dose. The extent of urinary excretion was low for both i.v. (0.35%-0.54%) and oral (0.13%-0.33%) doses. Further discussions on the chemical and microsomal stability were included. In conclusion, dose-independent absorption kinetics were observed at oral doses from 5 to 25 mg/kg in rats. Orally administered KR-31831 could be eliminated mainly by the liver metabolic pathway.

IT 571141-49-6, KR-31831

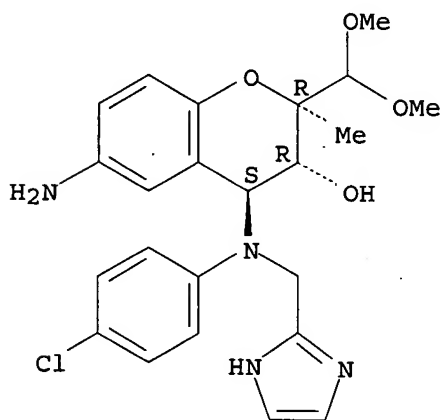
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacokinetics of antiangiogenic agent KR-31831 in rats)

RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:143140 HCAPLUS

DOCUMENT NUMBER: 140:181449

TITLE: Preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents

INVENTOR(S): Yi, Kyu Yang; Lee, Sun Kyung; Yoo, Sung-eun; Suh, Jee Hee; Kim, Nak-Jeong; Hwang, Sun Kyung; Lee, Byung-ho; Seo, Ho Won; Lee, Chong Ock; Choi, Sang-un

PATENT ASSIGNEE(S): Korea Research Institute of Chemical Technology, S. Korea

SOURCE: PCT Int. Appl., 93 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

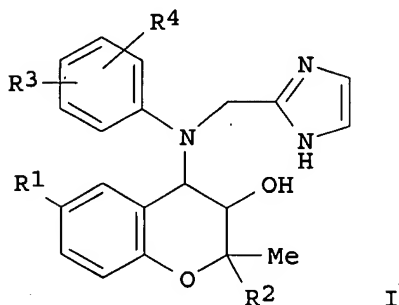
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014898	A1	20040219	WO 2003-KR1534	20030730
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

KR 2004014023	A	20040214	KR 2002-47189	20020809
CA 2493966	A1	20040219	CA 2003-2493966	20030730
AU 2003247213	A1	20040225	AU 2003-247213	20030730
EP 1546136	A1	20050629	EP 2003-784665	20030730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1675202	A	20050928	CN 2003-819195	20030730
JP 2006509725	T	20060323	JP 2004-527422	20030730
US 2005267188	A1	20051201	US 2005-523015	20050202
PRIORITY APPLN. INFO.:			KR 2002-47189	A 20020809
			WO 2003-KR1534	W 20030730
OTHER SOURCE(S):			CASREACT 140:181449; MARPAT 140:181449	
GI				



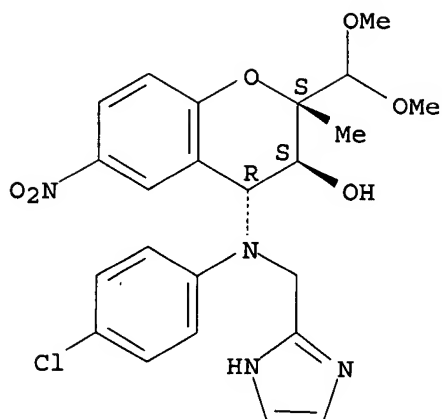
AB Imidazolylmethylaminobenzopyrans I [R1 = H, CN, NO2, NH2; R2 = dialkoxymethyl, alkylendioxyethyl; R3, R4 = H, Cl, Br, F, alkyl, CF3, OCF3, NO2, (un)substituted OH, CO2H] were prepared for use in the treatment of cancer, rheumatoid arthritis, and diabetic retinopathies through anti-angiogenic properties, and in the protection of heart and neuronal cells against ischemia-reperfusion injury or preserving organs. Thus, (2S,3R,4R)-3,4-dihydro-2-dimethoxymethyl-3,4-epoxy-2-methyl-6-nitro-2H-1-benzopyran was treated with N-(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)amine to give (2S,3R,4R)-I [R1 = NO2, R2 = CH(OMe)2, R3 = 4-Cl, R4 = H] which showed strong inhibition of HUVEC tube formation at 10  $\mu$ M.

IT 571141-37-2P 571141-39-4P 660404-73-9P  
660404-74-0P 660404-75-1P 660404-76-2P  
660404-77-3P 660404-78-4P 660404-80-8P  
660404-81-9P 660404-82-0P  
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
(preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents)

RN 571141-37-2 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

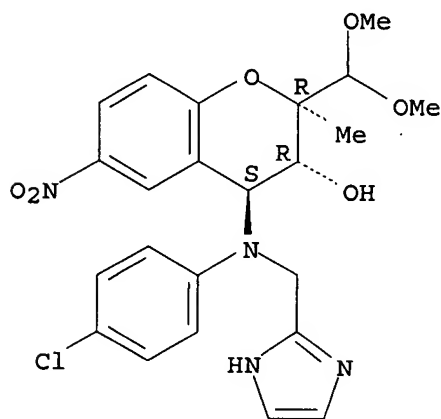
Absolute stereochemistry.



RN 571141-39-4 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

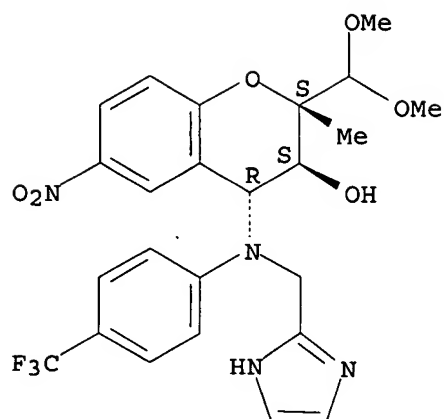


RN 660404-73-9 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethyl)phenyl]amino]-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

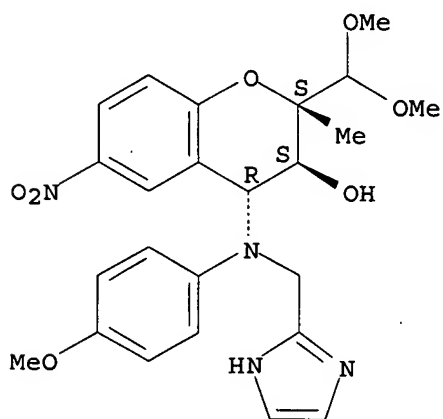




RN 660404-74-0 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

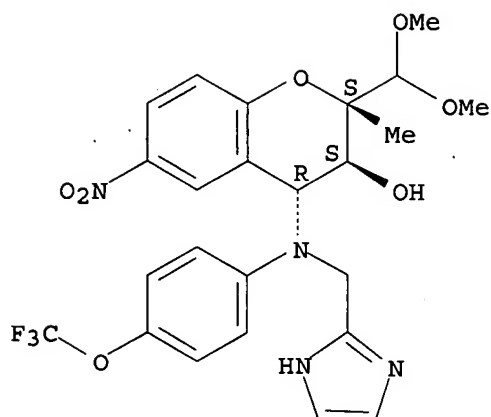
Absolute stereochemistry.



RN 660404-75-1 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-(trifluoromethoxy)phenyl)amino]-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

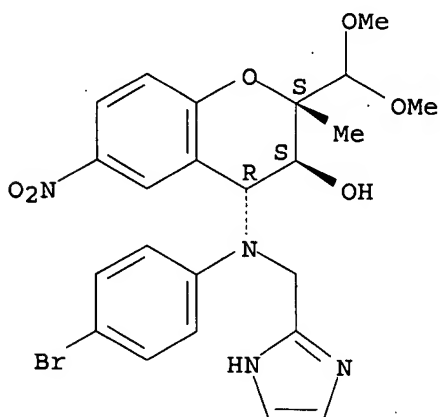
Absolute stereochemistry.



RN 660404-76-2 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

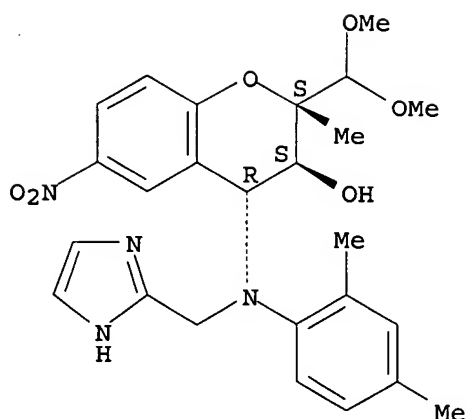
Absolute stereochemistry.



RN 660404-77-3 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-4-[(2,4-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

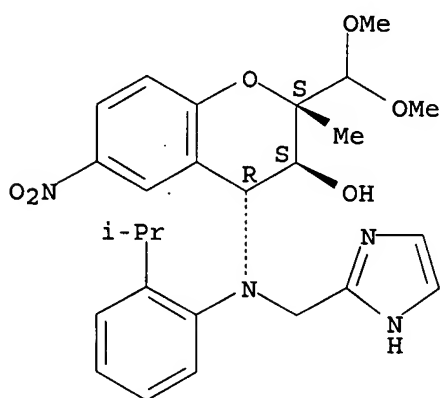
Absolute stereochemistry.



RN 660404-78-4 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl) [2-(1-methylethyl)phenyl]amino]-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

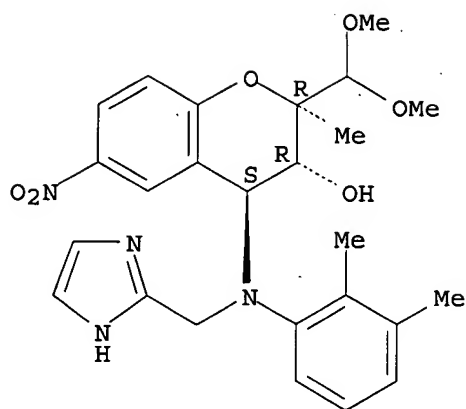
Absolute stereochemistry.



RN 660404-80-8 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-4-[(2,3-dimethylphenyl) (1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)-(9CI) (CA INDEX NAME)

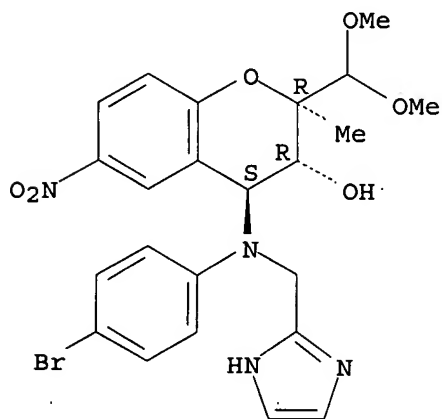
Absolute stereochemistry.



RN 660404-81-9 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

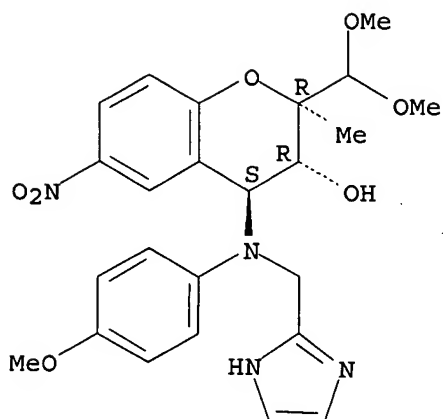
Absolute stereochemistry.



RN 660404-82-0 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 571141-36-1P 571141-38-3P 571141-47-4P  
 571141-49-6P 660404-90-0P 660404-91-1P  
 660404-92-2P 660404-93-3P 660404-94-4P  
 660404-95-5P

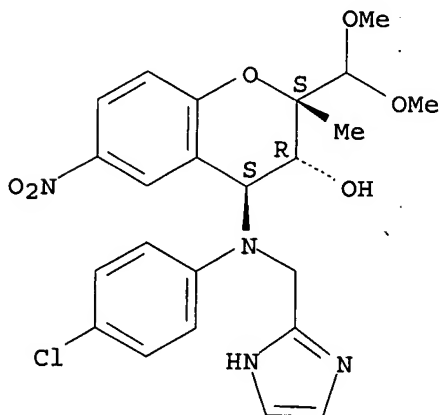
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU  
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES  
 (Uses)

(preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents)

RN 571141-36-1 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-  
 (dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3R,4S)- (9CI) (CA  
 INDEX NAME)

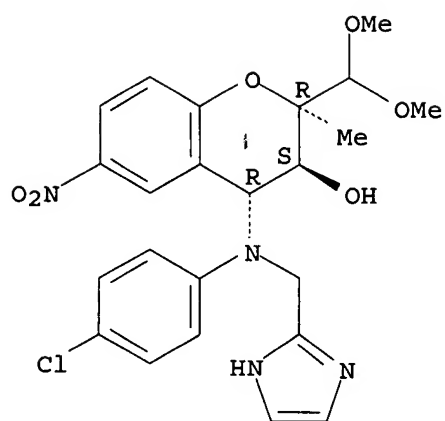
Absolute stereochemistry.



RN 571141-38-3 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-  
 (dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA  
 INDEX NAME)

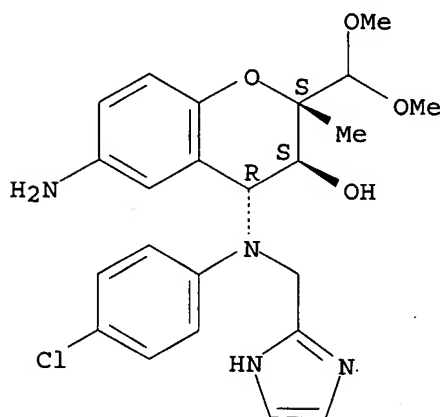
Absolute stereochemistry.



RN 571141-47-4 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

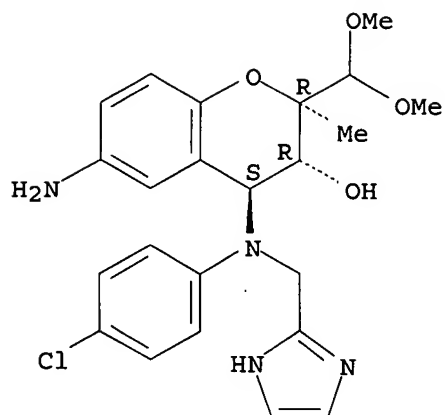
Absolute stereochemistry.



RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-(CA INDEX NAME)

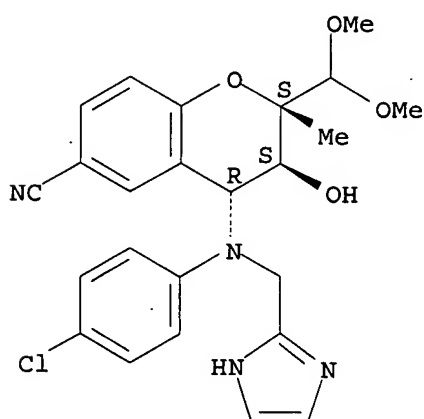
Absolute stereochemistry.



RN 660404-90-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-3-hydroxy-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

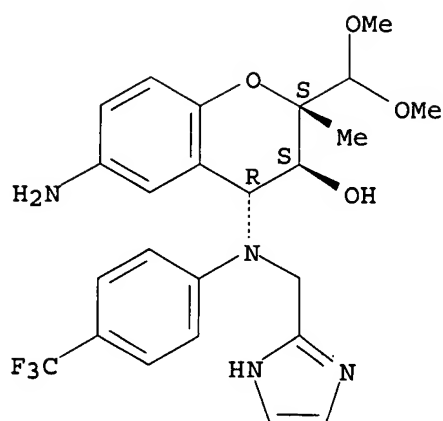
Absolute stereochemistry.



RN 660404-91-1 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-(trifluoromethyl)phenyl)amino]-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

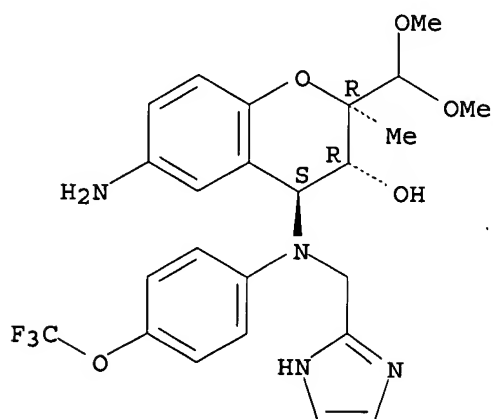
Absolute stereochemistry.



RN 660404-92-2 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl) [4-(trifluoromethoxy)phenyl]amino]-2-methyl-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

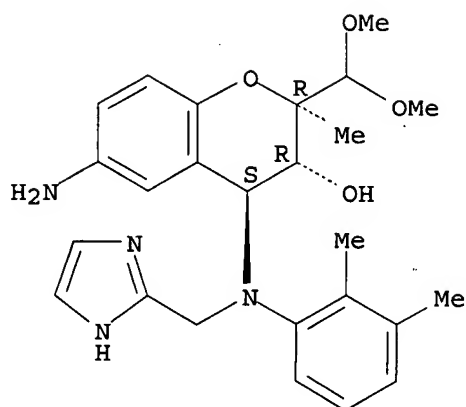


RN 660404-93-3 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-4-[(2,3-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

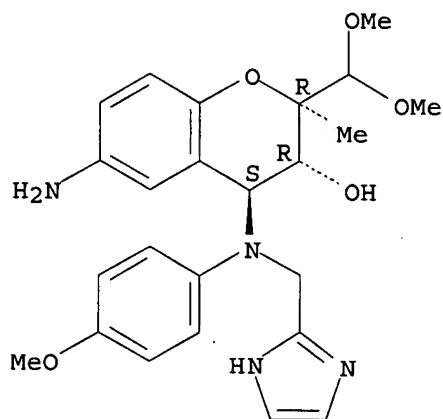




RN 660404-94-4 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl) (4-methoxyphenyl)amino]-2-methyl-, (2R,3R,4S) - (9CI)  
(CA INDEX NAME)

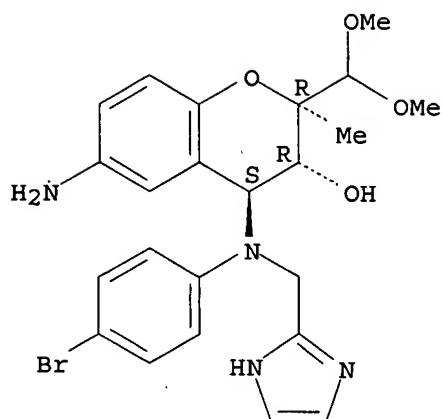
Absolute stereochemistry.



RN 660404-95-5 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-bromophenyl) (1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 660404-79-5P 660404-83-1P 660404-84-2P  
660404-89-7P

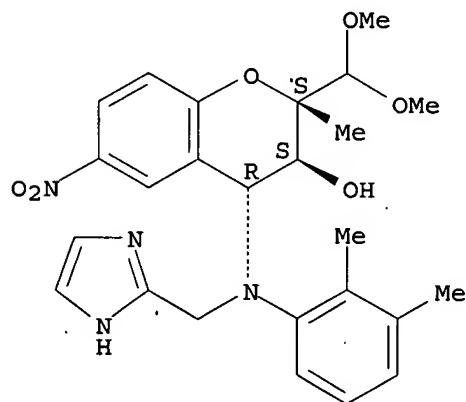
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use);  
BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent);  
USES (Uses)

(preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents)

RN 660404-79-5 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-4-[(2,3-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

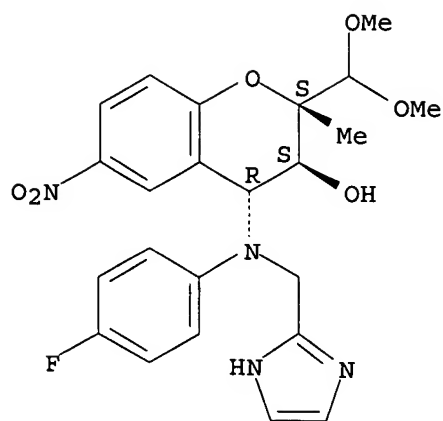
Absolute stereochemistry.



RN 660404-83-1 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

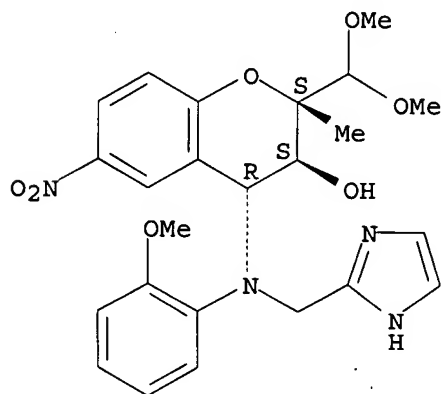
Absolute stereochemistry.



RN 660404-84-2 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(2-methoxyphenyl)amino]-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

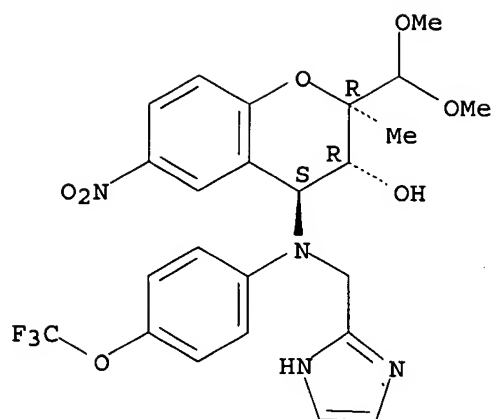
Absolute stereochemistry.



RN 660404-89-7 HCAPLUS

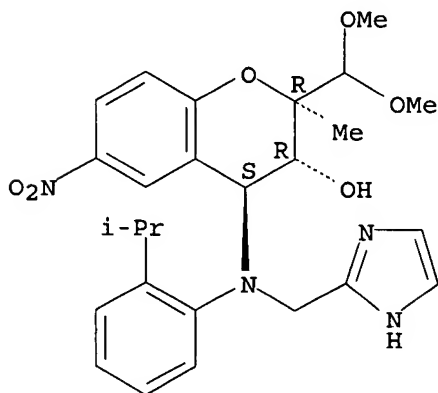
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



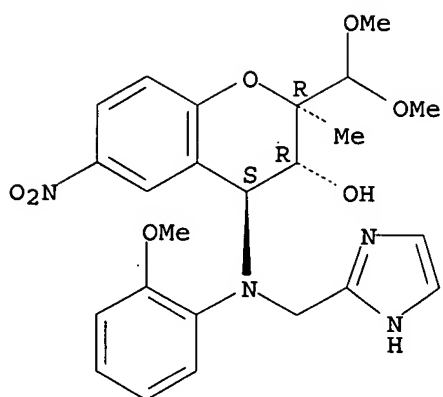
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 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (preparation of imidazolylmethylaminobenzopyrans as antiangiogenic agents)  
 RN 660404-85-3 HCAPLUS  
 CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl) [2-(1-methylethyl)phenyl]amino]-2-methyl-6-nitro-, (2R,3R,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 660404-86-4 HCAPLUS  
 CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl) (2-methoxyphenyl)amino]-2-methyl-6-nitro-, (2R,3R,4S)-(9CI) (CA INDEX NAME)

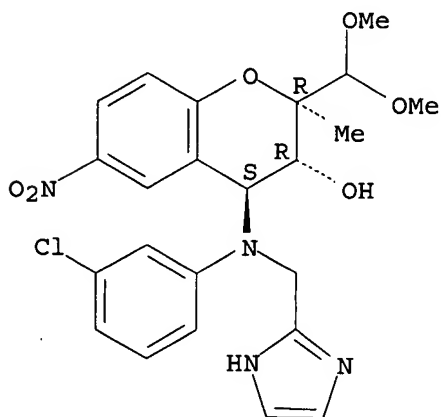
Absolute stereochemistry.



RN 660404-87-5 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(3-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

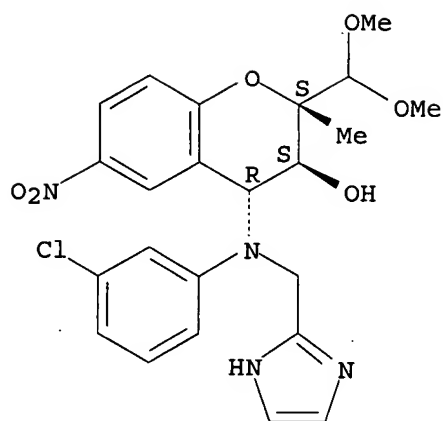
Absolute stereochemistry.



RN 660404-88-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(3-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

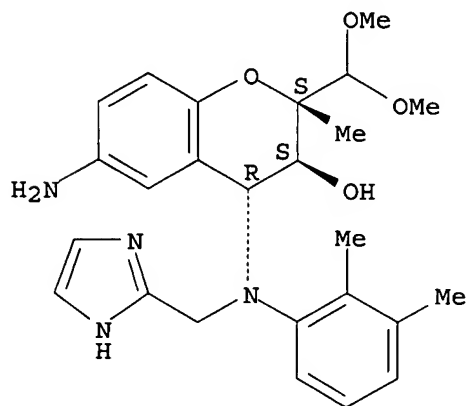
Absolute stereochemistry.



RN 660404-96-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-4-[(2,3-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-, (2S,3S,4R) - (9CI) (CA INDEX NAME)

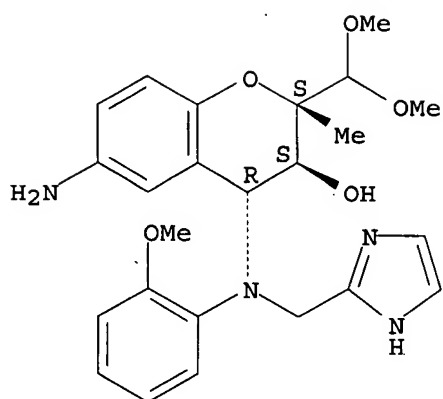
Absolute stereochemistry.



RN 660404-97-7 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(2-methoxyphenyl)amino]-2-methyl-, (2S,3S,4R) - (9CI) (CA INDEX NAME)

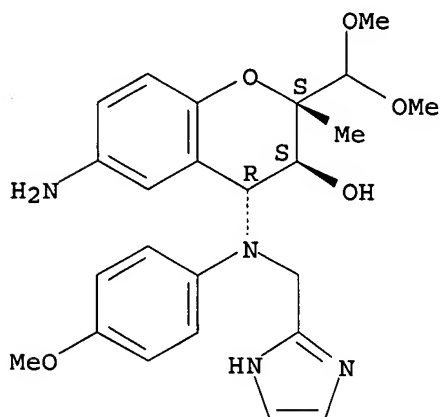
Absolute stereochemistry.



RN 660404-98-8 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-, (2S,3S,4R)- (9CI)  
(CA INDEX NAME)

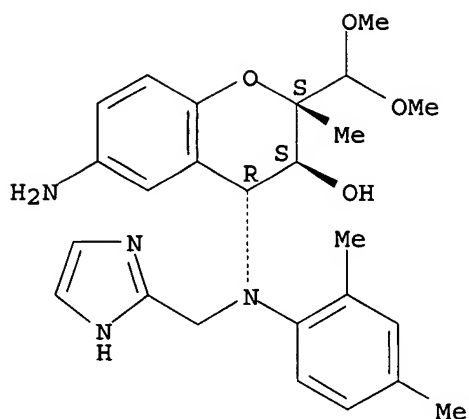
Absolute stereochemistry.



RN 660404-99-9 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-4-[(2,4-dimethylphenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

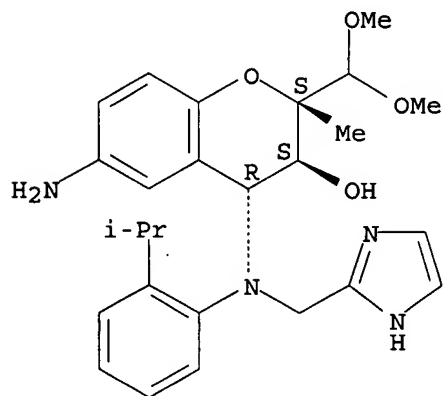
Absolute stereochemistry.



RN 660405-00-5 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[2-(1-methylethyl)phenyl]amino]-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

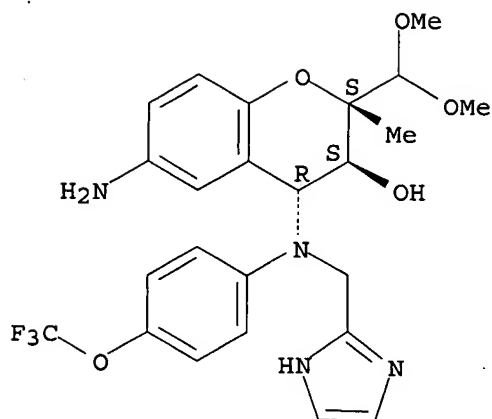


RN 660405-01-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

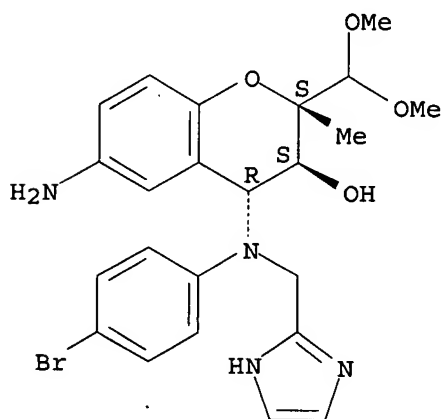




RN 660405-02-7 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

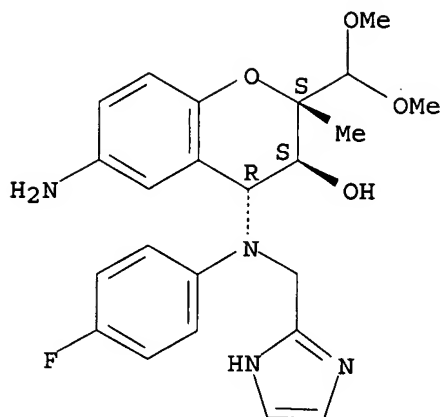
Absolute stereochemistry.



RN 660405-03-8 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:131575 HCAPLUS

DOCUMENT NUMBER: 141:81619

TITLE: Determination of a Novel Antiangiogenic Agent KR-31831 in Rat Plasma by Liquid Chromatography-Tandem Mass Spectrometry

AUTHOR(S): Kim, Sook Jin; Lee, Seung-Seok; Ji, Hye Young; Lee, Hong Il; Lee, Seonkyoung; Li, Kyu Yang; Yoo, Seong Eun; Hwang, Jeongsug; Lee, Hye Suk

CORPORATE SOURCE: College of Pharmacy, Drug Metabolism and Bioanalysis Laboratory, Wonkwang University, Iksan, S. Korea

SOURCE: Analytical Letters (2004), 37(2), 283-292

CODEN: ANALBP; ISSN: 0003-2719

PUBLISHER: Marcel Dekker, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A liquid chromatog.-tandem mass spectrometric (LC/MS/MS) method was developed for the determination of a new anti-angiogenic drug KR-31831 in rat plasma. KR-31831 and internal standard, KR-31543 were extracted from rat plasma

with CH<sub>2</sub>Cl<sub>2</sub> at basic pH. A reverse-phase LC separation was performed on Luna C8 column with the mixture of MeCN-ammonium formate (10 mM, pH 4.5) (67:33, volume/volume) as mobile phase. The detection of analytes was performed using an electrospray ionization tandem mass spectrometry in the multiple-reaction-monitoring mode. The standard curve was linear ( $r = 0.999$ ) over the concentration range of 1.0-500 ng/mL. The coefficient of variation of intra-

and inter-assay ranged from 0.8-3.9% and 1.4-3.9%, resp. The recoveries of KR-31831 ranged from 80.9% to 86.7%, with that of KR-31543 (internal standard) being  $99.2 \pm 2.7\%$ . The lower limits of quantification for KR-31831 was 1.0 ng/mL using 100  $\mu$ L plasma sample. This method was applied to the pharmacokinetic study of KR-31831 in rats.

IT 571141-49-6, KR 31831

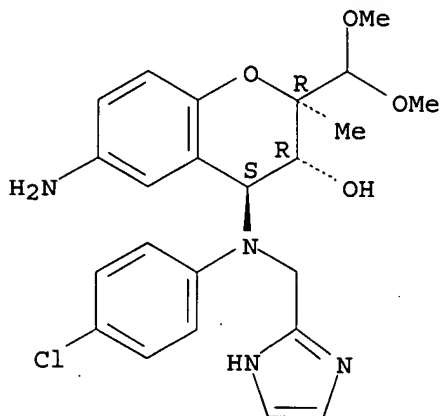
RL: ANT (Analyte); PKT (Pharmacokinetics); ANST (Analytical study); BIOL (Biological study)

(determination of a novel antiangiogenic agent KR-31831 in rat plasma by liquid chromatog.-tandem mass spectrometry)

RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S)-  
(CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:326008 HCAPLUS

DOCUMENT NUMBER: 139:143352

TITLE: Identification of a novel antiangiogenic agent;  
4-(N-Imidazol-2-ylmethyl)amino benzopyran analogues  
AUTHOR(S): Kim, Nakjeong; Lee, Sunkyung; Yi, Kyu Yang; Yoo, Sung-eun; Kim, Guncheol; Lee, Chong-OCK; Park, Sung Hee; Lee, Byung Ho

CORPORATE SOURCE: Medicinal Science Division, Korea Research Institute of Chemical Technology, Yoonsung-gu, Taejon, 305-600, S. Korea

SOURCE: Bioorganic & Medicinal Chemistry Letters (2003), 13(10), 1661-1663

CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 139:143352

AB A series of 4-(N-imidazol-2-ylmethyl)aminobenzopyran analogs, originally designed as KATP openers for ischemic diseases, showed antiangiogenic properties through the inhibition of HUVEC tube formation. Especially one of p-Cl substituted analogs completely inhibited HUVEC tube formation at 10  $\mu$ M and significantly inhibited tumor growth by 52% on A549 (human non small cell lung carcinoma) in nude mice xenografts without any significant side effects.

IT 571141-36-1P 571141-37-2P 571141-38-3P  
571141-39-4P 571141-40-7P 571141-41-8P  
571141-42-9P 571141-43-0P 571141-44-1P  
571141-45-2P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

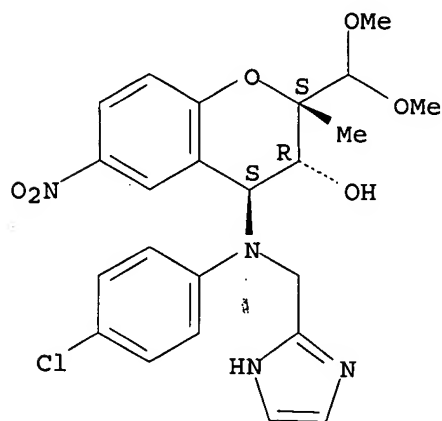
(identification of a novel antiangiogenic agent and structure-activity relationship 4-(N-imidazol-2-ylmethyl)amino benzopyran analogs)

10523015.trn

RN 571141-36-1 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3R,4S)- (9CI) (CA INDEX NAME)

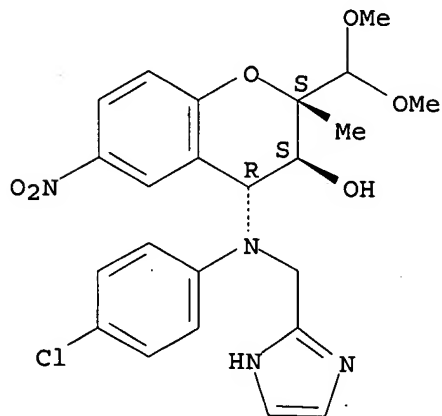
Absolute stereochemistry.



RN 571141-37-2 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2S,3S,4R)- (9CI) (CA INDEX NAME)

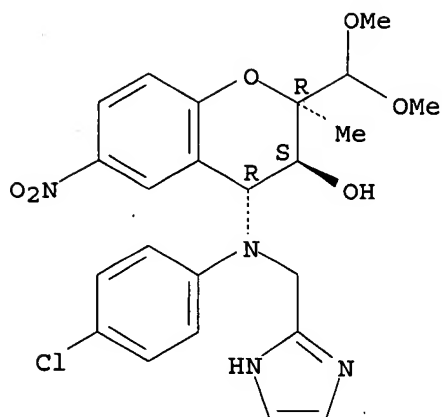
Absolute stereochemistry.



RN 571141-38-3 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

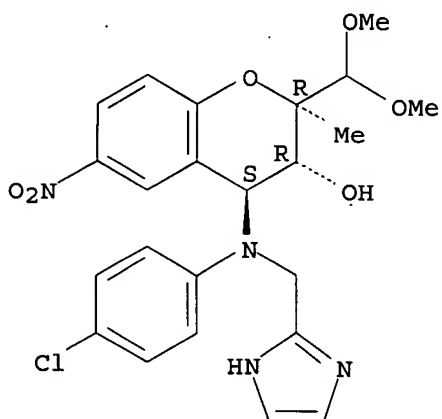
Absolute stereochemistry.



RN 571141-39-4 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 4-[(4-chlorophenyl) (1H-imidazol-2-ylmethyl) amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3R,4S)- (9CI) (CA INDEX NAME)

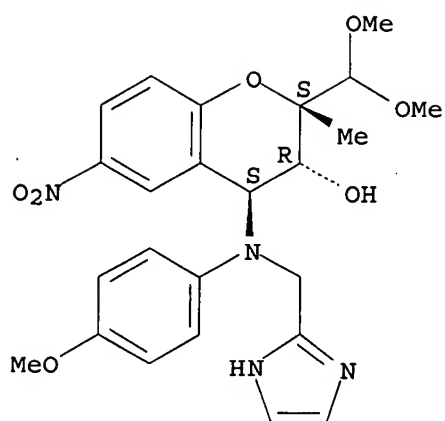
Absolute stereochemistry.



RN 571141-40-7 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl) (4-methoxyphenyl) amino]-2-methyl-6-nitro-, (2S,3R,4S)- (9CI) (CA INDEX NAME)

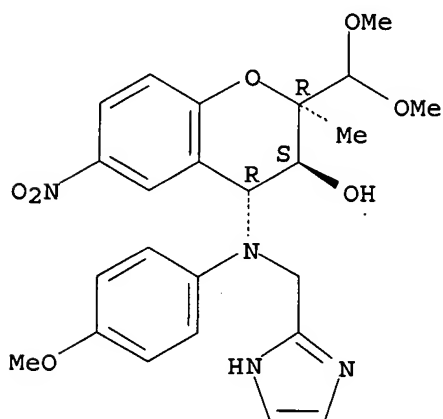
Absolute stereochemistry.



RN 571141-41-8 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

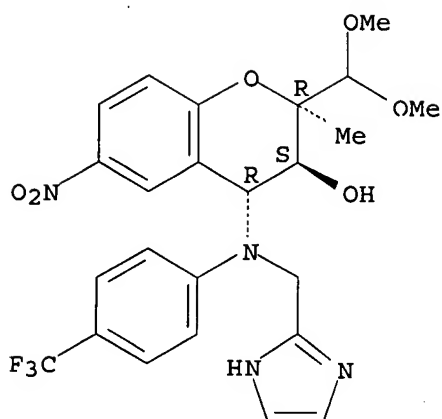
Absolute stereochemistry.



RN 571141-42-9 HCAPLUS

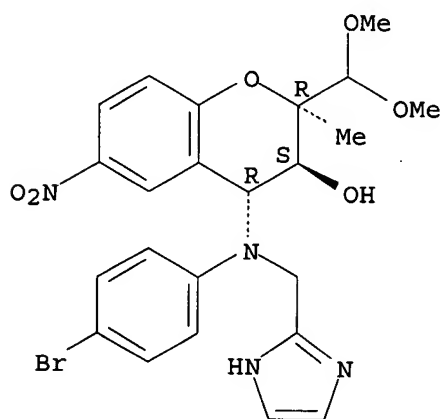
CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethyl)phenyl]amino]-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



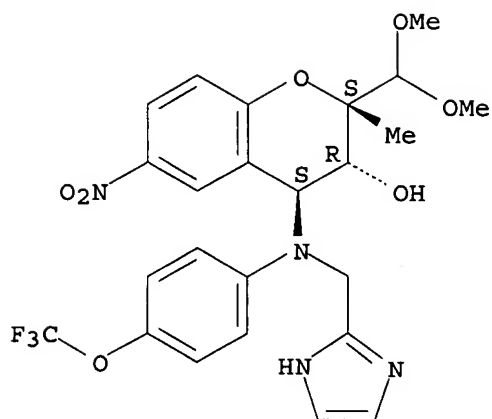
RN 571141-43-0 HCAPLUS  
 CN 2H-1-Benzopyran-3-ol, 4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-6-nitro-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 571141-44-1 HCAPLUS  
 CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-(trifluoromethoxy)phenyl)amino]-2-methyl-6-nitro-, (2S,3R,4S)- (9CI) (CA INDEX NAME)

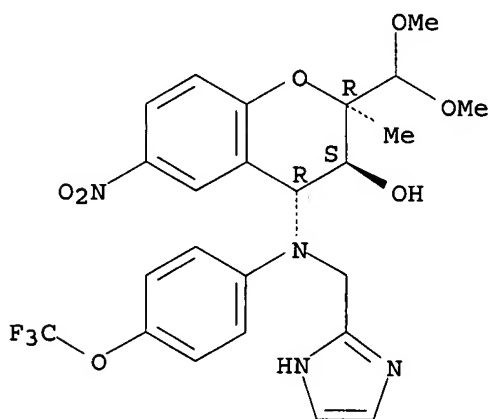
Absolute stereochemistry.



RN 571141-45-2 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl) [4-(trifluoromethoxy)phenyl]amino]-2-methyl-6-nitro-, (2R,3S,4R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 571141-46-3P 571141-47-4P 571141-48-5P  
571141-49-6P 571141-50-9P 571141-51-0P  
571141-52-1P 571141-53-2P 571141-54-3P  
571141-55-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

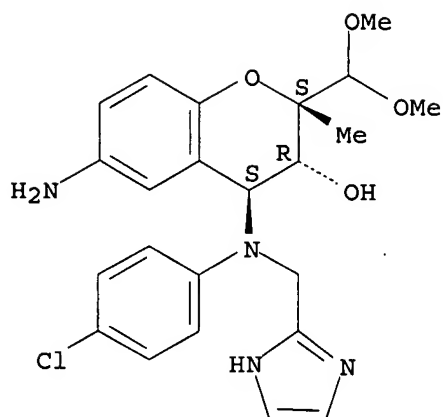
(identification of a novel antiangiogenic agent and structure-activity relationship 4-(N-imidazol-2-ylmethyl)amino benzopyran analogs)

RN 571141-46-3 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl) (1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2S,3R,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

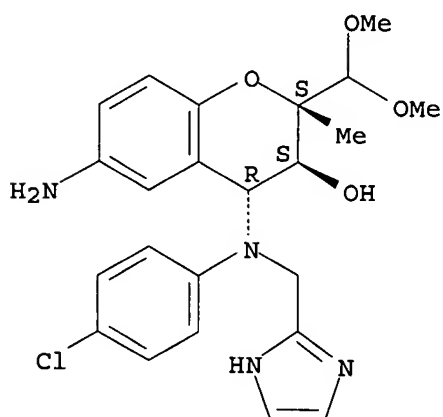




RN 571141-47-4 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2S,3S,4R)-(9CI) (CA INDEX NAME)

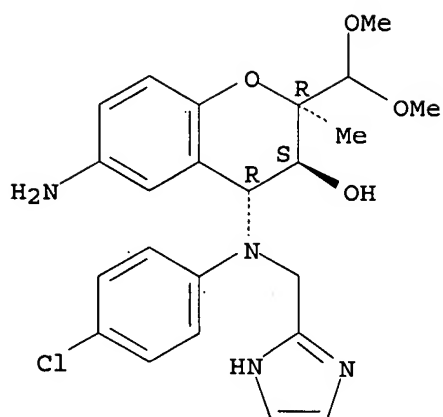
Absolute stereochemistry.



RN 571141-48-5 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3S,4R)-(9CI) (CA INDEX NAME)

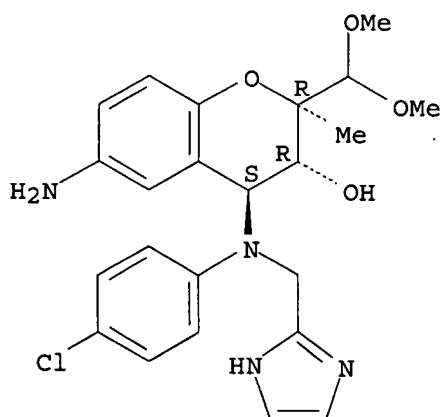
Absolute stereochemistry.



RN 571141-49-6 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3R,4S) - (CA INDEX NAME)

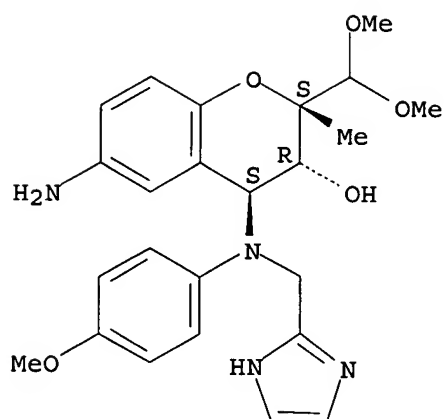
Absolute stereochemistry.



RN 571141-50-9 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-, (2S,3R,4S) - (9CI) (CA INDEX NAME)

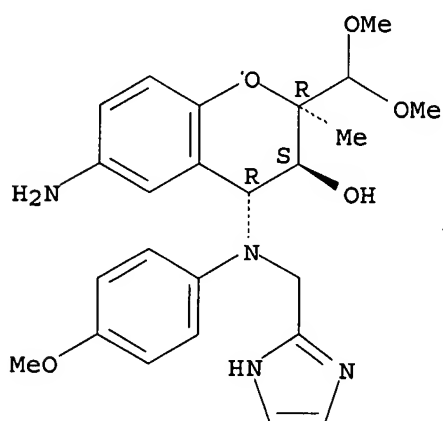
Absolute stereochemistry.



RN 571141-51-0 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)(4-methoxyphenyl)amino]-2-methyl-, (2R,3S,4R)- (9CI)  
(CA INDEX NAME)

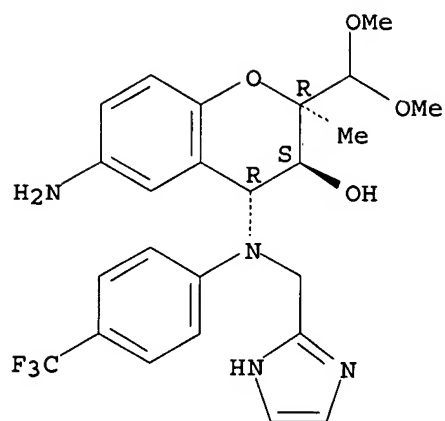
Absolute stereochemistry.



RN 571141-52-1 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethyl)phenyl]amino]-2-methyl-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

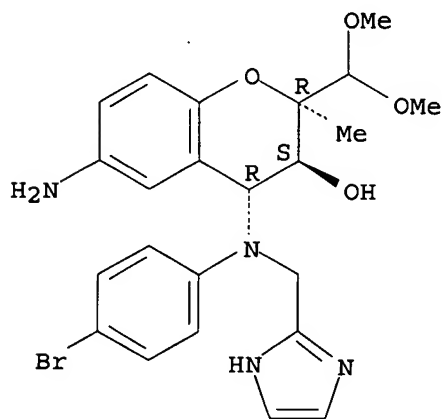
Absolute stereochemistry.



RN 571141-53-2 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-4-[(4-bromophenyl)(1H-imidazol-2-ylmethyl)amino]-2-(dimethoxymethyl)-3,4-dihydro-2-methyl-, (2R,3S,4R)-(9CI) (CA INDEX NAME)

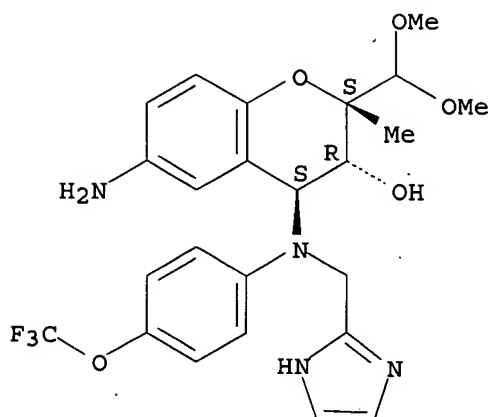
Absolute stereochemistry.



RN 571141-54-3 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)]-4-(trifluoromethoxy)phenylamino]-2-methyl-, (2S,3R,4S)-(9CI) (CA INDEX NAME)

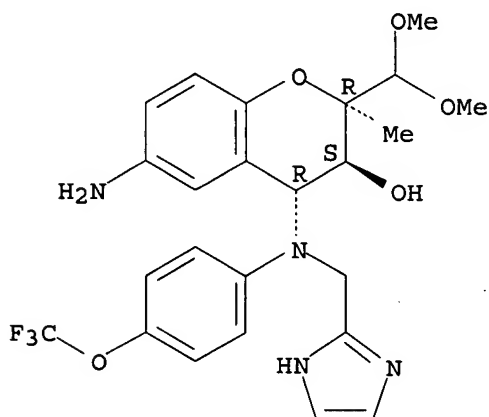
Absolute stereochemistry.



RN 571141-55-4 HCAPLUS

CN 2H-1-Benzopyran-3-ol, 6-amino-2-(dimethoxymethyl)-3,4-dihydro-4-[(1H-imidazol-2-ylmethyl)[4-(trifluoromethoxy)phenyl]amino]-2-methyl-, (2R,3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L9 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:845162 HCAPLUS

DOCUMENT NUMBER: 139:576

TITLE: Pharmacologic profile of the selective mitochondrial-KATP opener BMS-191095 for treatment of acute myocardial ischemia

AUTHOR(S): Grover, Gary J.; Atwal, Karnail S.

CORPORATE SOURCE: Cardiovascular and Metabolic Diseases Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Pennington, NJ, USA

SOURCE: Cardiovascular Drug Reviews (2002), 20(2), 121-136

CODEN: CDREEA; ISSN: 0897-5957

PUBLISHER: Neva Press  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB ATP-sensitive potassium channel (KATP) openers as a class protect ischemic myocardium. The protective effects are independent of vasodilator activity and effects on action potential shortening, actions typically associated with sarcolemmal KATP activation. BMS-191095 is a novel mitochondrial KATP opener which protects ischemic myocardium while having no electrophysiol. or vasodilator effects (determined in vitro and in vivo). The cardioprotective effects were determined in isolated rat hearts subjected to ischemia and reperfusion. Protective effects were deduced from increased time to contracture formation during ischemia, improved reperfusion recovery of contractile function, and reduced reperfusion lactate dehydrogenase release. The cardioprotective effects of BMS-191095 were observed at concns. at which this compound selectively opened cardiac mitochondrial KATP channels. This effect was consistent with the pharmacol. profile of this agent. The protective effects were abolished by mitochondrial KATP inhibition. Unlike first-generation KATP openers, BMS-191095 is expected to protect ischemic myocardium with little hemodynamic sequelae and without any proarrhythmic potential. BMS-191095 is potentially useful clin. as a cardioprotective agent. It is also a useful tool for basic research.

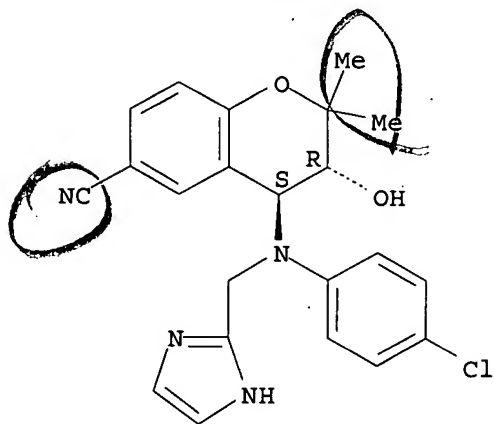
IT 166095-21-2, BMS-191095

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)  
(mitochondrial-KATP opener BMS-191095 pharmacol. profile for treatment of acute myocardial ischemia)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:749914 HCAPLUS

DOCUMENT NUMBER: 138:297322

TITLE: In vivo characterization of the mitochondrial selective KATP opener (3R)-trans-4-[(4-chlorophenyl)-N-(1H-imidazol-2-ylmethyl)dimethyl]-2H-1-benzopyran-6-

carbonitrile monohydrochloride (BMS-191095):  
cardioprotective, hemodynamic, and  
electrophysiological effects

AUTHOR(S): Grover, Gary J.; D'Alonzo, Albert J.; Darbenzio,  
Raymond B.; Parham, Charles S.; Hess, Thomas A.;  
Bathala, Mohinder S.

CORPORATE SOURCE: Metabolic and Cardiovascular Drug Discovery,  
Bristol-Myers Squibb Pharmaceutical Research  
Institute, Pennington, NJ, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics  
(2002), 303(1), 132-140  
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental  
Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

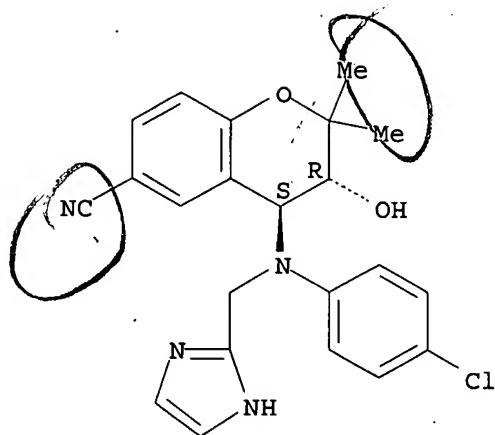
AB Recent studies have shown the importance of mitochondrial ATP-sensitive  
potassium channels (KATP) in cardioprotection, and studies in vitro have  
shown that the benzopyran analog BMS-191095 is a selective mitochondrial  
KATP opener with cardioprotective activity. The goal of this study was to  
show selective cardioprotection for BMS-191095 in vivo without hemodynamic  
or cardiac electrophysiol. effects expected for nonselective KATP openers.  
BMS-191095 reduced infarct size in anesthetized dogs (90-min ischemia +  
5-h reperfusion) in a dose-dependent manner (ED25 = 0.4 mg/kg i.v.) with  
efficacious plasma concns. of 0.3 to 1.0  $\mu$ M, which were consistent with  
potency in vitro. None of the doses of BMS-191095 tested caused any  
effect on peripheral or coronary hemodynamic status. Further studies in  
dogs showed no effects of BMS-191095 on cardiac conduction or action  
potential configuration within the cardioprotective dose range. In a  
programmed elec. stimulation model, BMS-191095 showed no proarrhythmic  
effects, which is consistent with its lack of effects on cardiac  
electrophysiol. status. BMS-191095 is a potent and efficacious  
cardioprotectant that is devoid of hemodynamic and cardiac electrophysiol.  
side effects of first generation KATP openers, which open both sarcolemmal  
and mitochondrial KATP. Selective opening or activation of mitochondrial  
KATP seems to be a potentially effective strategy for developing well  
tolerated and efficacious KATP openers.

IT 166095-21-2, BMS-191095  
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(in vivo characterization of mitochondrial selective KATP opener  
BMS-191095 in relation to cardioprotective, hemodynamic, and  
electrophysiol. effects)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-  
ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN  
 ACCESSION NUMBER: 2002:293433 HCAPLUS  
 DOCUMENT NUMBER: 136:304080  
 TITLE: Diazoxide, pinacidil, nicorandil and/or BMS 191095 for treatment of apoptotic cell death in cardiac and neuronal cells  
 INVENTOR(S): Marban, Eduardo; O'Rourke, Brian; Akao, Massaharu; Ohler, Andreas  
 PATENT ASSIGNEE(S): Johns Hopkins University, USA  
 SOURCE: PCT Int. Appl., 23 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002030411	A2	20020418	WO 2001-US31992	20011015 <--
WO 2002030411	A8	20020711		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002013174	A5	20020422	AU 2002-13174	20011015 <--
US 2002091144	A1	20020711	US 2001-977558	20011015 <--
US 6521617	B2	20030218		

PRIORITY APPLN. INFO.: US 2000-240267P P 20001013  
 WO 2001-US31992 W 20011015

AB New methods are provided for treating against apoptotic cell death, including apoptotic cardiac and neuronal cells. Therapies of the invention includes administration of a mitochondrial oxidizer compound to a subject in need thereof, such as a subject suffering from or susceptible to stroke, heart attack, brain or spinal cord trauma, or chronic conditions that can resulting apoptotic cell death such as a



neurodegenerative disease and diabetes. Compds. used for treatment of apoptotic cell death included diazoxide, pinacidil, nicorandil, and/or BMS 191095.

IT 166095-21-2, BMS 191095

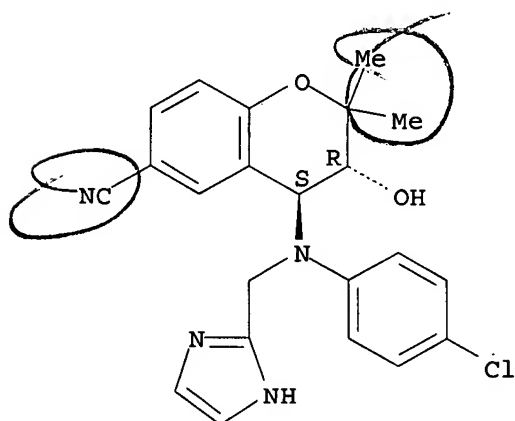
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(diazoxide, pinacidil, nicorandil and/or BMS 191095 for treatment of apoptotic cell death in cardiac and neuronal cells)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:214387 HCAPLUS

DOCUMENT NUMBER: 137:72948

TITLE: Differential action of KR-31378, a novel potassium channel activator, on cardioprotective and hemodynamic effects

AUTHOR(S): Lee, Byung Ho; Seo, Ho Won; Yoo, Sung-Eun; Kim, Sun-Ok; Lim, Hong; Shin, Hwa Sup

CORPORATE SOURCE: Screening and Toxicology Research Center, Korea Research Institute of Chemical Technology, Taejon, 305-343, S. Korea

SOURCE: Drug Development Research (2001), 54(4), 182-190

CODEN: DDREDK; ISSN: 0272-4391

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The cardioprotective and hemodynamic effects of KR-31378, a highly cardioselective ATP-sensitive potassium channel activator with minimal hypotensive effect, were evaluated in rats and dogs, and compared with those of BMS-191095 and lemakalim. KR-31378 did not show any significant effect on methoxamine-induced aortic constriction up to doses of 300  $\mu$ M, whereas BMS 191095 produced a moderately potent relaxant effect ( $IC_{50}$ : 9.0  $\mu$ M). In conscious rats, KR-31378 slightly increased blood pressure only at high dose (100 mg/kg, iv), unlike BMS-191095 that dose-dependently decreased blood pressure (ED<sub>20</sub>: 2.03 mg/kg). In anesthetized beagle dogs, KR-31378 was approx. 100-fold less potent than BMS-191095 for most hemodynamic parameters (iv ED<sub>20</sub> for blood pressure)

lowering: 33.7 and 0.37 mg/kg, resp.). In anesthetized rats subjected to 45-min coronary occlusion and 90-min reperfusion, KR-31378 (iv) dose-dependently reduced the infarct zone from 58.6% to 42.1%, 36.6%, and 34.3% for 0.1, 0.3, and 1.0 mg/kg, resp. ( $P < 0.05$ ), the effects being comparable to those of BMS 191095. In anesthetized beagle dogs that underwent 2-h occlusion followed by 4.5-h reperfusion, KR-31378 (2 mg/kg, iv infusion) markedly reduced the infarct zone from 48.7% in controls to 19.1% at a dose of 2 mg/kg ( $P < 0.05$ ). The reduction in infarct zone afforded by KR-31378 in rats was inhibited by pretreatment with selective ATP-sensitive potassium channel blockers, sodium 5-hydroxydecanoate and glibenclamide. These results indicate that KR-31378 is a potent cardioprotective agent with potentially minimal hypotensive effects. Thus, it could be potentially useful in the prevention and treatment of acute myocardial infarction.

IT 166095-21-2, BMS 191095

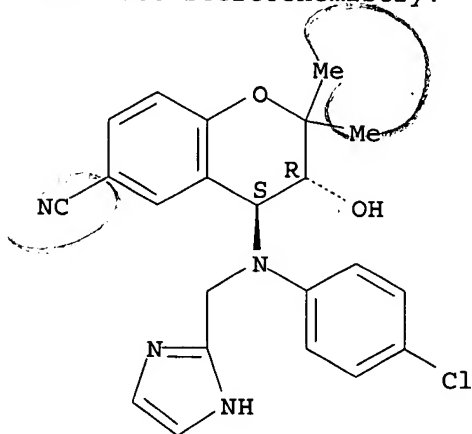
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(differential action of KR-31378, a novel potassium channel activator, on cardioprotective and hemodynamic effects)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:380223 HCAPLUS

DOCUMENT NUMBER: 135:175010

TITLE: Pharmacologic characterization of BMS-191095, a mitochondrial KATP opener with no peripheral vasodilator or cardiac action potential shortening activity

AUTHOR(S): Grover, Gary J.; D'Alonzo, Albert J.; Garlid, Keith D.; Bajgar, Robert; Lodge, Nicholas J.; Sleph, Paul G.; Darbenzio, Raymond B.; Hess, Thomas A.; Smith, Mark A.; Paucek, Petr; Atwal, Karnail S.

CORPORATE SOURCE: Metabolic and Cardiovascular Diseases Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Pennington, NJ, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics

(2001), 297(3), 1184-1192

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous work described ATP-sensitive K<sup>+</sup> channel (KATP) openers (e.g., BMS-180448), which retain the cardioprotective activity of agents such as cromakalim while being significantly less potent as vasodilators. In this study, we describe the pharmacol. profile of BMS-191095, which is devoid of peripheral vasodilating activity while retaining glyburide-reversible cardioprotective activity. In isolated rat hearts subjected to 25 min of global ischemia and 30 min of reperfusion, BMS-191095 increased the time to onset of ischemic contracture with an EC<sub>25</sub> of 1.5  $\mu$ M, which is comparable to 4.7  $\mu$ M and 3.0  $\mu$ M for cromakalim and BMS-180448, resp. Comparisons of cardioprotective and vasorelaxant potencies in vitro and in vivo showed BMS-191095 to be significantly more selective for cardioprotection with virtually no effect on peripheral smooth muscle, whereas cromakalim showed little selectivity. In addition to increasing the time to the onset of contracture, BMS-191095 improved postischemic recovery of function and reduced lactate dehydrogenase release in the isolated rat hearts. The cardioprotective effects of BMS-191095 were abolished by glyburide and sodium 5-hydroxydecanoate (5-HD). BMS-191095 did not shorten action potential duration in normal or hypoxic myocardium within its cardioprotective concentration range nor did it activate sarcolemmal KATP current ( $\leq 30$   $\mu$ M). BMS-191095 opened cardiac mitochondrial KATP with a K<sub>1/2</sub> of 83 nM, and this was abolished by glyburide and 5-HD. These results show that the cardioprotective effects of BMS-191095 are dissociated from peripheral vasodilator and cardiac sarcolemmal KATP activation. Agents like BMS-191095 may owe their cardioprotective selectivity to selective mitochondrial KATP activation.

IT 166095-21-2, BMS-191095

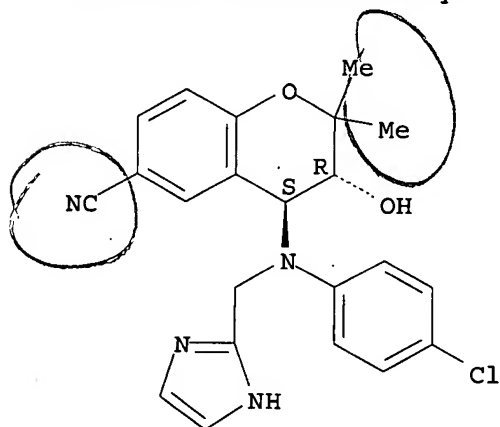
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacol. characterization of mitochondrial KATP opener BMS-191095)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS

## RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:510838 HCAPLUS

DOCUMENT NUMBER: 131:295097

TITLE: Cardiosensitive Antiischemic ATP-Sensitive Potassium Channel (KATP) Openers. 6. Effect of Modifications at C6 of Benzopyranyl Cyanoguanidines

AUTHOR(S): Ding, Charles Z.; Rovnyak, George C.; Misra, Raj N.; Grover, Gary J.; Miller, Arthur V.; Ahmed, Syed Z.; Kelly, Yolanda; Normandin, Diane E.; Sleph, Paul G.; Atwal, Karnail S.

CORPORATE SOURCE: The Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA

SOURCE: Journal of Medicinal Chemistry (1999), 42(18), 3711-3717

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effect on potency and selectivity of modifications at the C6 position of the cardioprotective KATP opener BMS-180448 is described. Structure-activity studies show that a variety of electron-withdrawing groups (ketone, sulfone, sulfonamide, etc.) are tolerated for cardioprotective activity as measured by EC25 values for an increase in time to the onset of contracture in globally ischemic rat hearts. Changes made to the sulfonamido substituent indicate that compds. derived from secondary lipophilic amines are preferred for good cardioprotective potency and selectivity. The diisobutylsulfonamide analog (I) (EC25 = 0.04  $\mu$ M) is the most potent compound of this series. The cardiac selectivity of I results from a combination of reduced vasorelaxant potency and enhanced cardioprotective potency relative to the potent vasodilating KATP openers (e.g., cromakalim). I is over 4 orders of magnitude more cardiac selective than cromakalim. These results support the hypothesis that the cardioprotective and vasorelaxant properties of KATP openers follow distinct structure-activity relationships. The mechanism of action of I appears to involve opening of the cardiac KATP as its cardioprotective effects are abolished by the KATP blocker glyburide.

IT 166095-21-2, BMS 191095

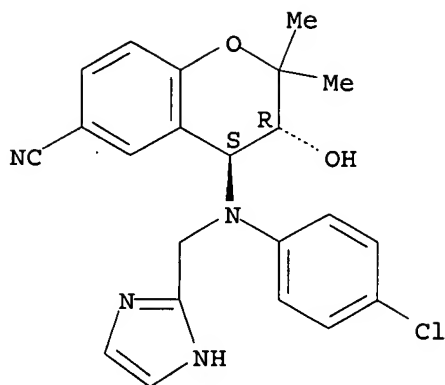
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation and cardioprotective structure-activity relations of benzopyranylcyanoguanidines as ATP-sensitive potassium channel openers)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1998:755870 HCAPLUS

DOCUMENT NUMBER: 130:13916

TITLE: Preparation of 4-(arylamino)benzopyrans and analogs as cardiovascular agents

INVENTOR(S): Rovnyak, George C.; Atwal, Karnail S.; Santafianos, Dinos P.; Ding, Charles Z.

PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA

SOURCE: U.S., 43 pp., Cont.-in-part of U. S. Ser. No. 134,034, abandoned.

CODEN: USXXAM

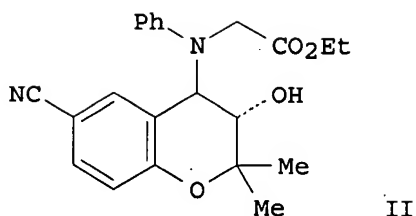
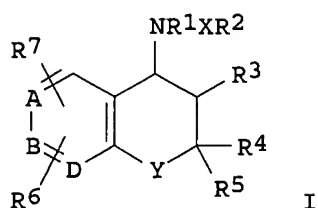
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5837702	A	19981117	US 1994-296341	19940830 <--
CA 2132766	A1	19950408	CA 1994-2132766	19940923 <--
FI 9404624	A	19950408	FI 1994-4624	19941004 <--
NO 9403763	A	19950410	NO 1994-3763	19941006 <--
ZA 9407833	A	19950413	ZA 1994-7833	19941006 <--
AU 9474461	A	19950427	AU 1994-74461	19941006 <--
HU 72447	A2	19960429	HU 1994-2884	19941006 <--
CN 1107473	A	19950830	CN 1994-116854	19941007 <--
JP 07242650	A	19950919	JP 1994-244216	19941007 <--
PRIORITY APPLN. INFO.: GI			US 1993-134034	B2 19931007



AB Title compds. [I; A, B, D = C atom (sic), or 1 of A, B, D = N or NO and the others = C atom (si); X = alkyl; XR2 = H, aryl, heterocyclyl when R1 = heterocyclyl; Y = bond, CH2, C, O, S NR8; R8 = H, alkyl, haloalkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)aryl; R1 = aryl, heterocyclyl; R2 = CO2R8, SR8, OR8, cyano, heterocyclyl, amino, aminocarbonyl, (cyclic) phosphate alkyl ester, etc.; R3 = H, OH, O2CR8; R4, R5 = H, alkyl, aralkyl; R4R5C = 5-7 membered carbocyclyl; R6 = H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, cycloalkylalkyl, cyano, NO2, COR8, CO2R8, CF3, alkylthio, alkylsulfinyl, alkylsulfonyl, (cyclic) phosphate alkyl ester, halo, amino, alkoxy, OCF3, OCH2CF3, tetrazolyl, imidazolyl, oxazolyl, triazolyl, etc.; R7 = H, alkyl, OH, alkoxy, amino, NHCOR8, cyano, NO2; n = 1-3], were prepared as potassium channel activators useful as antiischemics (no data). Thus, 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-benzopyran-6-carbonitrile and PhNHCH2CO2Et were stirred with Mg(ClO4)2 in MeCN for 2 days to give 53% title compound (II).

IT 166095-11-0P 166095-23-4P 166095-53-0P

166095-95-0P 166095-96-1P 166095-99-4P

166096-00-0P 166096-01-1P

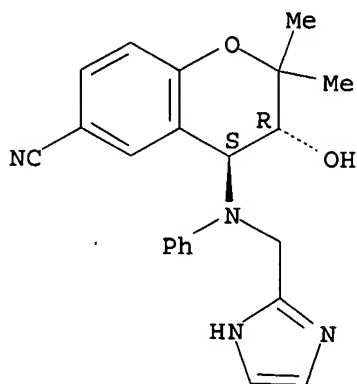
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of 4-(arylamino)benzopyrans and related compds. as cardiovascular agents)

RN 166095-11-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



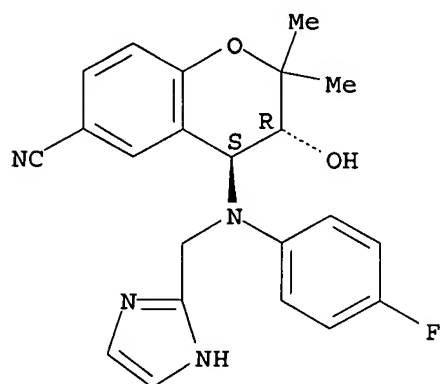
RN 166095-23-4 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA

10523015.trn

INDEX NAME)

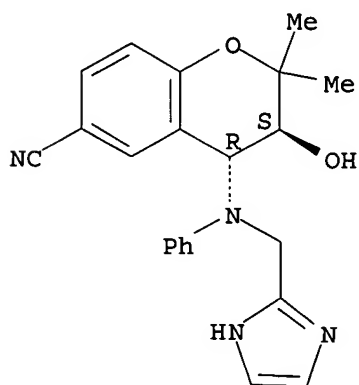
Absolute stereochemistry.



RN 166095-53-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3S,4R)- (9CI) (CA INDEX NAME)

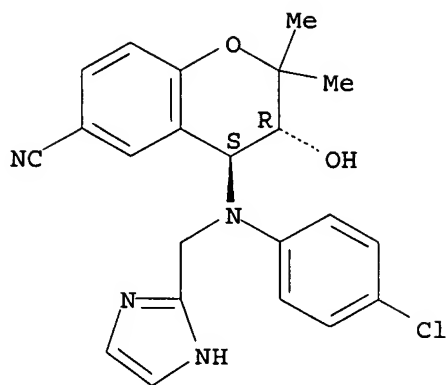
Absolute stereochemistry.



RN 166095-95-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, monohydrochloride, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



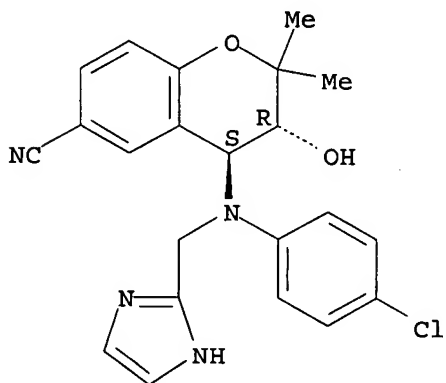
● HCl

RN 166095-96-1 HCAPLUS  
 CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, sulfate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 166095-21-2  
 CMF C22 H21 Cl N4 O2

Absolute stereochemistry.

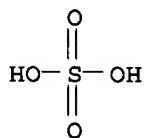


CM 2

CRN 7664-93-9  
 CMF H2 O4 S



10523015.trn

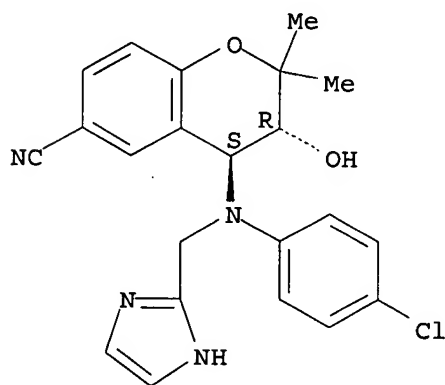


RN 166095-99-4 HCAPLUS  
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

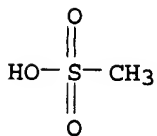
CRN 166095-21-2  
CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



CM 2

CRN 75-75-2  
CMF C H4 O3 S



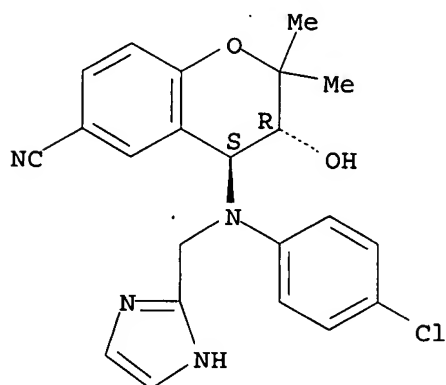
RN 166096-00-0 HCAPLUS  
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, phosphate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 166095-21-2  
CMF C22 H21 Cl N4 O2

10523015.trn

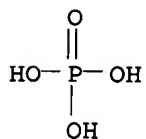
Absolute stereochemistry.



CM 2

CRN 7664-38-2

CMF H3 O4 P



RN 166096-01-1 HCAPLUS

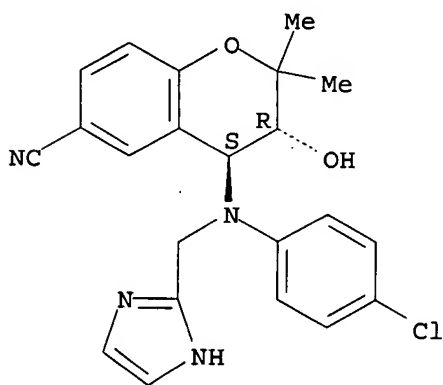
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, mononitrate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 166095-21-2

CMF C22 H21 Cl N4 O2

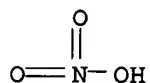
Absolute stereochemistry.



CM 2

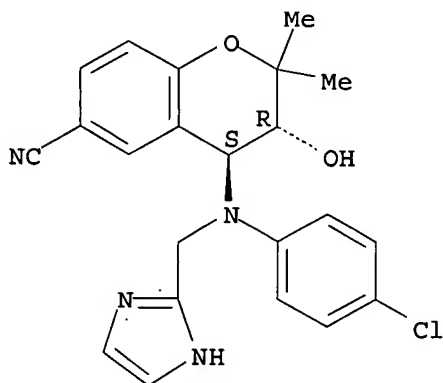
CRN 7697-37-2

CMF H N O3



IT 166095-21-2P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(preparation of 4-(arylamino)benzopyrans and related compds. as  
cardiovascular agents)  
RN 166095-21-2 HCAPLUS  
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-  
ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA  
INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

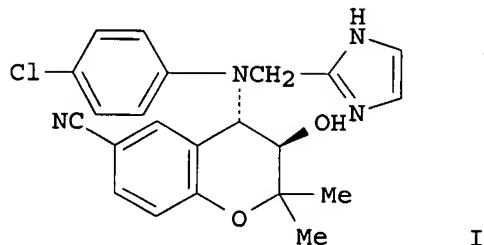
L9 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN  
ACCESSION NUMBER: 1997:342006 HCAPLUS  
DOCUMENT NUMBER: 127:50637  
TITLE: Process for preparing 4-arylamino benzopyrans and  
related compounds  
INVENTOR(S): Kronenthal, David R.; Mueller, Richard H.; Godfrey,  
Jollie D., Jr.  
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA  
SOURCE: U.S., 11 pp.  
CODEN: USXXAM  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 5629429  
 PRIORITY APPLN. INFO.:  
 OTHER SOURCE(S):  
 GI

A 19970513 US 1995-486111  
 US 1995-486111  
 CASREACT 127:50637; MARPAT 127:50637

19950607 <--  
 19950607



AB Title compds. are prepared by treating an arylamine with 2 equivalent of a base,

followed by treatment with an epoxybenzopyran. Use of a Li base, such as BuLi, LiN(CHMe<sub>2</sub>)<sub>2</sub>, or LiN(SiMe<sub>3</sub>)<sub>2</sub>, gives predominantly the trans-arylamino(hydroxy)benzopyran, whereas use of a Grignard reagent, such as EtMgBr or EtMgCl, gives predominantly the cis-products. The products are useful as antiischemic agents and K channel activators (no data). Thus, 4-ClC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub> was treated with 2-imidazolecarboxaldehyde to give N-(4-chlorophenyl)-N-(2-imidazolylmethyl)amine which was treated with (1aR-cis)-1a,7b-dihydro-2,2-dimethyl-2H-oxireno[c]-1-benzopyran-6-carbonitrile in presence of LiN(SiMe<sub>3</sub>)<sub>2</sub> to give the title compound I.

IT 166095-21-2P

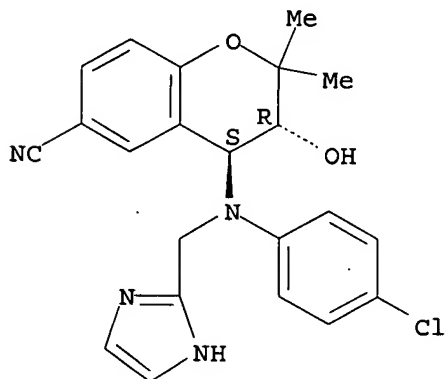
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(stereoselective preparation of arylaminobenzopyrans by use of base)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 166095-95-0P 186180-85-8P 190952-97-7P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

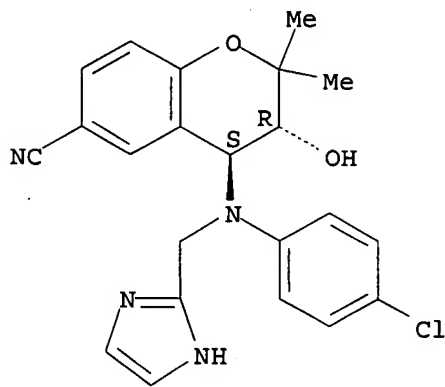
(stereoselective preparation of arylaminobenzopyrans by use of base)

10523015.trn

RN 166095-95-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, monohydrochloride, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

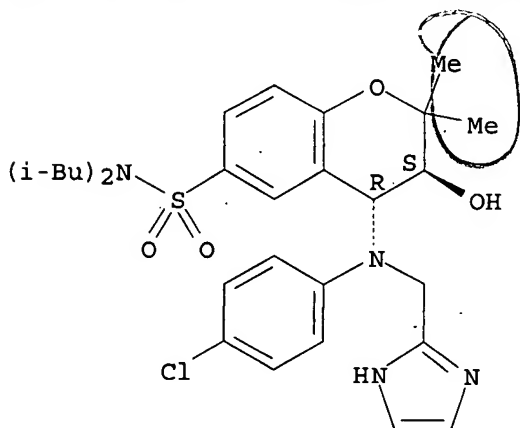


● HCl

RN 186180-85-8 HCAPLUS

CN 2H-1-Benzopyran-6-sulfonamide, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-N,N-bis(2-methylpropyl)-, (3S-trans)- (9CI) (CA INDEX NAME)

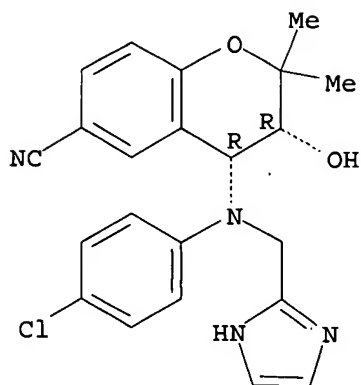
Absolute stereochemistry. Rotation (-).



RN 190952-97-7 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R-cis)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:113299 HCAPLUS

DOCUMENT NUMBER: 126:117866

TITLE: Preparation of N-(4-chlorophenyl)-N'-(sulfonamido-4-benzopyranyl)-N''-cyanoguanidines and analogs as potassium channel activators

INVENTOR(S): Ding, Charles Z.; Atwal, Karnail S.

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: Eur. Pat. Appl., 55 pp.

CODEN: EPXXDW

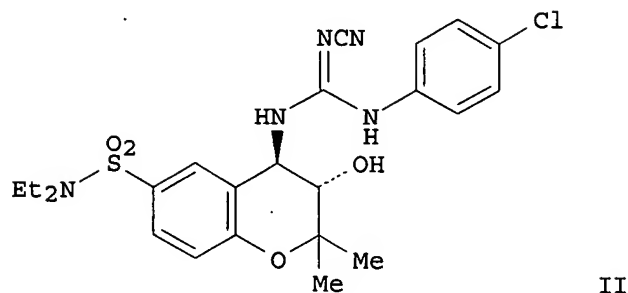
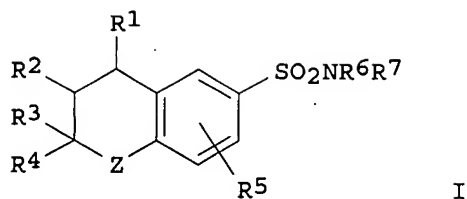
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 747374	A1	19961211	EP 1996-109023	19960605 <--
EP 747374	B1	20011212		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 5869478	A	19990209	US 1995-481007	19950607 <--
AT 210650	T	20011215	AT 1996-109023	19960605 <--
PT 747374	T	20020531	PT 1996-109023	19960605 <--
ES 2169174	T3	20020701	ES 1996-109023	19960605 <--
CA 2178353	A1	19961208	CA 1996-2178353	19960606 <--
AU 9654762	A	19961219	AU 1996-54762	19960606 <--
AU 714432	B2	20000106		
JP 09003035	A	19970107	JP 1996-146288	19960607 <--
PRIORITY APPLN. INFO.:			US 1995-481007	A 19950607
OTHER SOURCE(S):	CASREACT 126:117866; MARPAT 126:117866			
GI				



AB Title compds. [I; R1 = NR10C(:X)NR8R9, NR12Z1R13, etc.; R2 = H, OH, alkanoyloxy, etc.; R3,R4 = H or (ar)alkyl; R3R4 = atoms to complete a carbocyclic ring; R6,R7 = H, (un)substituted alkyl, aryl, etc.; NR6R7 = heterocyclyl; R5R6 = atoms to complete a ring; R8 = aryl(alkyl), heterocyclyl(alkyl); R9 = H or alkyl; R10 = H, alkyl, aryl(alkyl), etc.; R12 = aryl or heterocyclyl; R13 = H, CO2H, alkoxycarbonyl, CCONH2, etc.; X = NCN, O, S; Z = bond, CH2, CO, O, S, (alkyl)imino, etc.; Z1 = bond, alkylene] were prepared as potassium channel activators (no data). Thus, 4-BrC6H4OH was etherified by HOCMe2C.tplbond.CH and the cyclized product converted in 5 steps to (3S-trans)-4-amino-N,N-diethyl-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-sulfonamide which was condensed with 4-ClC6H4NHC(:S)NHCN to give title compound II.

IT 186180-82-5P 186180-83-6P 186180-85-8P  
186255-44-7P

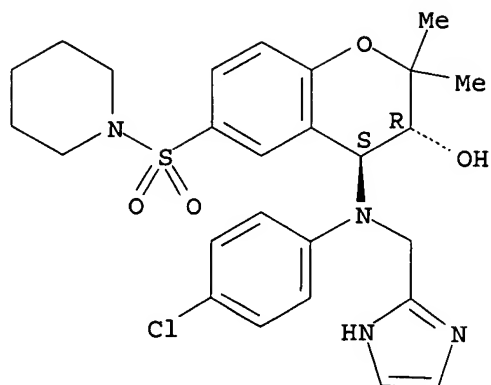
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of N-(4-chlorophenyl)-N'-(sulfonamido-4-benzopyranyl)-N''-cyanoguanidines and analogs as potassium channel activators)

RN 186180-82-5 HCAPLUS

CN Piperidine, 1-[[4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-yl]sulfonyl]-, monohydrochloride, (3R-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

10523015.trn

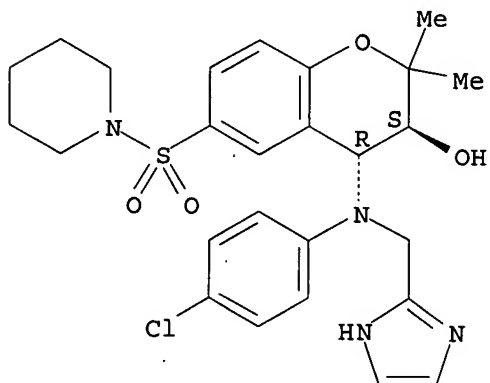


● HCl

RN 186180-83-6 HCAPLUS

CN Piperidine, 1-[[4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-yl]sulfonyl]-, monohydrochloride, (3S-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



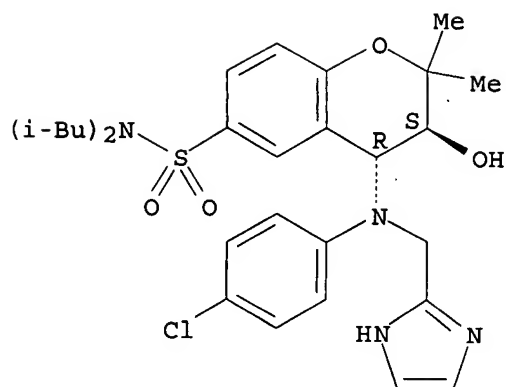
● HCl

RN 186180-85-8 HCAPLUS

CN 2H-1-Benzopyran-6-sulfonamide, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-N,N-bis(2-methylpropyl)-, (3S-trans)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

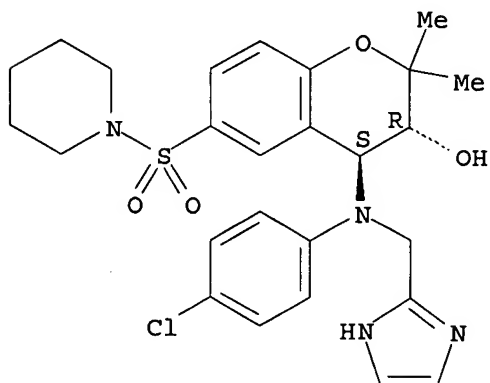




RN 186255-44-7 HCAPLUS

CN Piperidine, 1-[[[(3R,4S)-4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-yl]sulfonyl]- (9CI)  
(CA INDEX NAME).

Absolute stereochemistry. Rotation (+).



L9 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:48231 HCAPLUS

DOCUMENT NUMBER: 126:126687

TITLE: A highly selective ATP-dependent potassium channel opener mimics ischemic preconditioning protection in isolated human atrium

AUTHOR(S): Carr, C. S.; Yellon, D. M.

CORPORATE SOURCE: Hatter Institute, University College London Hospitals, London, UK

SOURCE: Medical Science Research (1996), 24(10), 651-654

CODEN: MSCREJ; ISSN: 0269-8951

PUBLISHER: Chapman &amp; Hall

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The KATP channel has been implicated in the mechanism of ischemic preconditioning. We examined the effects of BMS 191095, a highly selective KATP channel opener, either alone or with glibenclamide (KATP channel blocker), on human atrium. Isolated human atrial trabecula superfused

with oxygenated Tyrode's solution and paced at 1 Hz underwent one of four protocols prior to 90 min hypoxic substrate-free perfusion at 3 Hz (simulated ischemia), followed by 120 min of reoxygenation with substrate at 1 Hz (reoxygenation). Preconditioning (PC) consisted of 3 min simulated ischemia and 7 min reoxygenation. The exptl. endpoint was recovery of contractile function, presented as percentage of baseline function. BMS ( $45.8\% \pm 4.4$ ) and PC ( $50.5\% \pm 3.6$ ) produced similar functional recoveries following 120 min reperfusion; significantly different to controls ( $20.8\% \pm 3.5$ , ANOVA). Glibenclamide abolished the BMS protection ( $20.8\% \pm 4.2$ ). These results suggest that ischemic preconditioning in humans may occur via a KATP channel opening effect.

IT 166095-21-2, BMS 191095

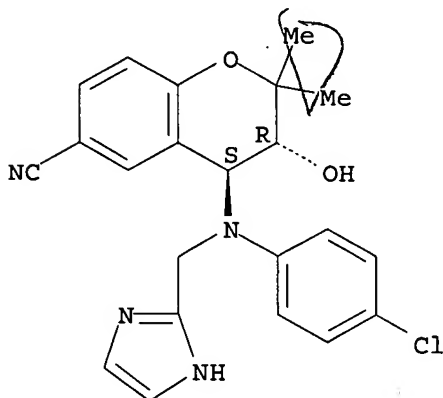
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(a highly selective ATP-dependent potassium channel opener mimics ischemic preconditioning protection in isolated human atrium)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:744328 HCAPLUS

DOCUMENT NUMBER: 126:98837

TITLE: Cardiosselective Antiischemic ATP-Sensitive Potassium Channel (KATP) Openers. 5. Identification of 4-(N-Aryl)-Substituted Benzopyran Derivatives with High Selectivity

AUTHOR(S): Rovnyak, George C.; Ahmed, Syed Z.; Baird, Anne J.; Ding, Charles Z.; Dzwonczyk, Steven; Ferrara, Francis N.; Humphreys, W. Griffith; Grover, Gary J.; McLaughlin, Lee G.; et al.

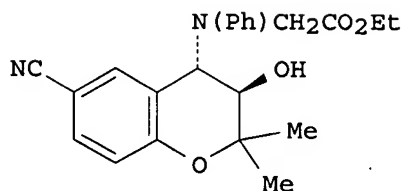
CORPORATE SOURCE: Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA

SOURCE: Journal of Medicinal Chemistry (1997), 40(1), 24-34

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



I

AB This paper describes our studies aimed at the discovery of structurally distinct analogs of the cardioprotective KATP opener BMS-180448 with improved selectivity for the ischemic myocardium. The starting compound I showed good cardioprotective potency and excellent selectivity compared to BMS-180448 and the first-generation KATP opener cromakalim. The structure-activity studies indicate that increasing the size of the alkyl ester leads to diminished potency as does its replacement with a variety of other groups (nitrile, Me sulfone). Replacement of the Et ester of I with an imidazole gave the best compound (BMS-191095) of this series which maintains the potency and selectivity of its predecessor I. The results described in this publication further support that there is no correlation between vasorelaxant and cardioprotective potencies of KATP openers. BMS-191095 is over 20- and 4000-fold more selective for the ischemic myocardium than BMS-180448 and cromakalim, resp. The selectivity for the ischemic myocardium is achieved by reduction of vasorelaxant potency rather than enhancement in antiischemic potency. As for cromakalim and BMS-180448, the cardioprotective effects of BMS-191095 are inhibited by cotreatment with the KATP blocker glyburide, indicating that the KATP opening is involved in its mechanism of cardioprotection. With its good oral bioavailability (47%) and plasma elimination half-life (3 h) in rats, BMS-191095 offers an excellent candidate to investigate the role of residual vasorelaxant potency of 2 toward its cardioprotective activity in vivo.

IT 166095-11-0P 166095-21-2P, BMS 191095  
 166095-23-4P 185690-27-1P

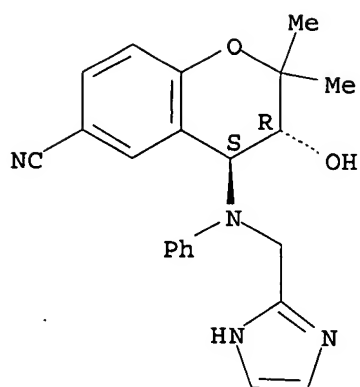
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation and structure-activity relations of benzopyran derivs. as cardioselective antiischemic ATP-sensitive potassium channel openers)

RN 166095-11-0 HCAPLUS

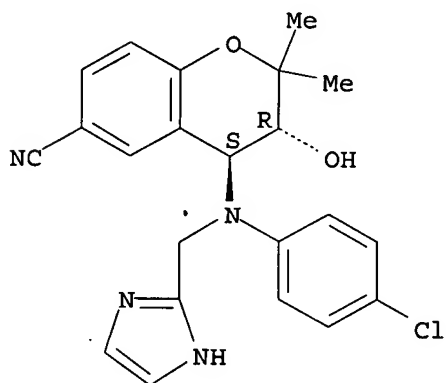
CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



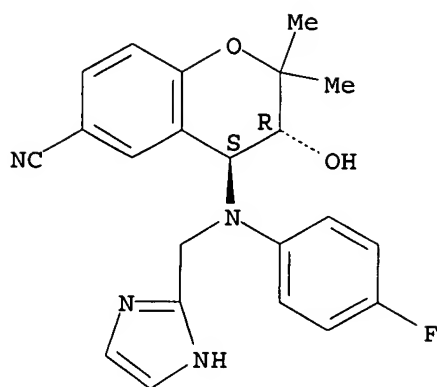
RN 166095-21-2 HCAPLUS  
 CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 166095-23-4 HCAPLUS  
 CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

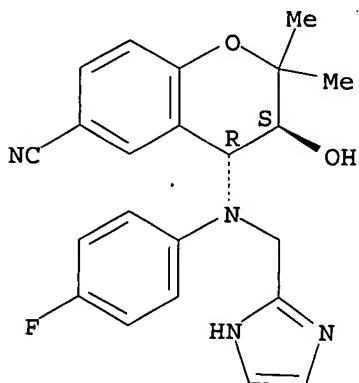
Absolute stereochemistry.



RN 185690-27-1 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3S-trans)- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:728999 HCAPLUS

DOCUMENT NUMBER: 123:339740

TITLE: Preparation of 4-(arylamino)benzopyrans and related compounds as cardiovascular agents.

INVENTOR(S): Rovnyak, George C.; Atwal, Karnail; Santafianos, Dinos P.; Ding, Charles Z.

PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA

SOURCE: Eur. Pat. Appl., 66 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

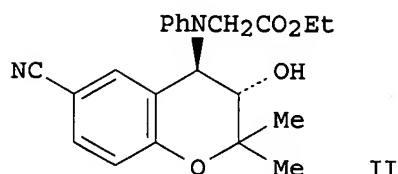
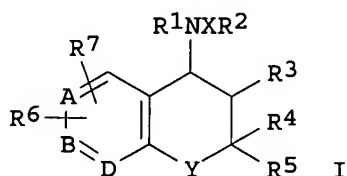
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 648758	A1	19950419	EP 1994-306814	19940916 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

CA 2132766	A1	19950408	CA 1994-2132766	19940923 <--
FI 9404624	A	19950408	FI 1994-4624	19941004 <--
NO 9403763	A	19950410	NO 1994-3763	19941006 <--
ZA 9407833	A	19950413	ZA 1994-7833	19941006 <--
AU 9474461	A	19950427	AU 1994-74461	19941006 <--
HU 72447	A2	19960429	HU 1994-2884	19941006 <--
CN 1107473	A	19950830	CN 1994-116854	19941007 <--
JP 07242650	A	19950919	JP 1994-244216	19941007 <--
PRIORITY APPLN. INFO.:			US 1993-134034	A 19931007
OTHER SOURCE(S):	MARPAT	123:339740		
GI				



AB Title compds. [I; A, B, D = C, or 1 of A, B, D = N, NO and the others = C; X = alkyl; XR2 = H, aryl, heterocyclyl when R1 = heterocyclyl; Y = bond, CH2, C(O), O, S N(R8); R8 = H, alkyl, haloalkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)aryl; R1 = aryl, heterocyclyl; R2 = CO2R8, SR8, OR8, cyano, heterocyclyl, amino, aminocarbonyl, (cyclic) phosphate alkyl ester, etc.; R3 = H, OH, O2CR8; R4, R5 = H, alkyl, aralkyl; R4R5C = 5-7 membered carbocyclyl; R6 = H, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, cycloalkylalkyl, cyano, NO2, COR8, CO2R8, CF3, alkylthio, alkylsulfinyl, alkylsulfonyl, (cyclic) phosphate alkyl ester, halo, amino, alkoxy, OCF3, OCH2CF3, tetrazolyl, imidazolyl, oxazolyl, triazolyl, etc.; R7 = H, alkyl, OH, alkoxy, amino, NHCOR8, cyano, NO2; n = 1-3], were prepared as potassium channel activators useful as antiischemics (no data). Thus, 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-benzopyran-6-carbonitrile and PhNHCH2CO2Et were stirred with Mg(ClO4)2 in MeCN for 2 days to give 53% title compound (II).

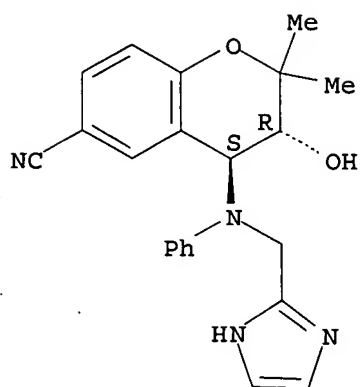
IT 166095-11-0P 166095-23-4P 166095-53-0P  
166095-95-0P 166095-96-1P 166095-99-4P  
166096-00-0P 166096-01-1P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(preparation of 4-(arylamino)benzopyrans and related compds. as cardiovascular agents)

RN 166095-11-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

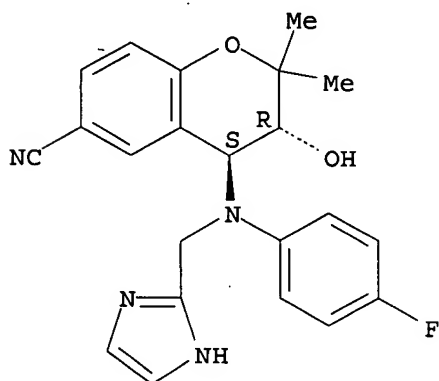
Absolute stereochemistry.



RN 166095-23-4 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-fluorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

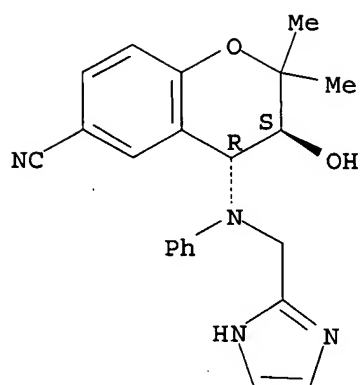


RN 166095-53-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 3,4-dihydro-3-hydroxy-4-[(1H-imidazol-2-ylmethyl)phenylamino]-2,2-dimethyl-, (3S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

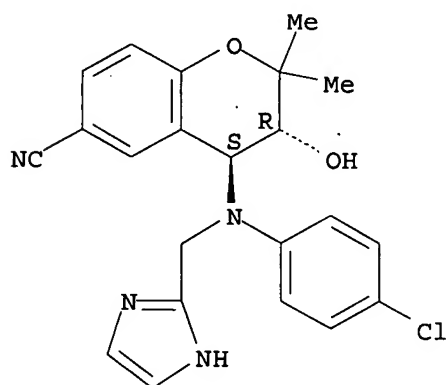
10523015.trn



RN 166095-95-0 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, monohydrochloride, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

RN 166095-96-1 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, sulfate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

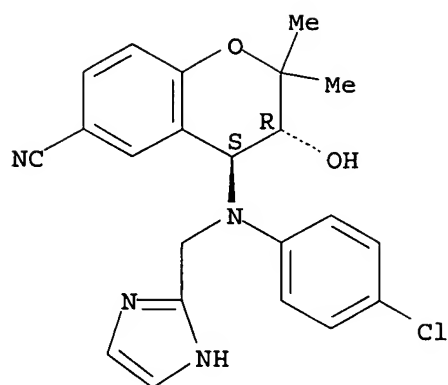
CRN 166095-21-2

CMF C22 H21 Cl N4 O2

Absolute stereochemistry.



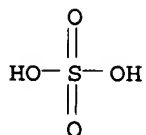
10523015.trn



CM 2

CRN 7664-93-9

CMF H2 O4 S



RN 166095-99-4 HCAPLUS

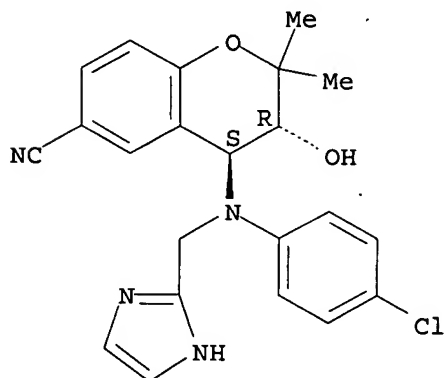
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, monomethanesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 166095-21-2

CMF C22 H21 Cl N4 O2

Absolute stereochemistry.

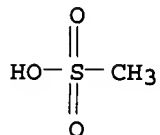


10523015.trn

CM 2

CRN 75-75-2

CMF C H4 O3 S



RN 166096-00-0 HCAPLUS

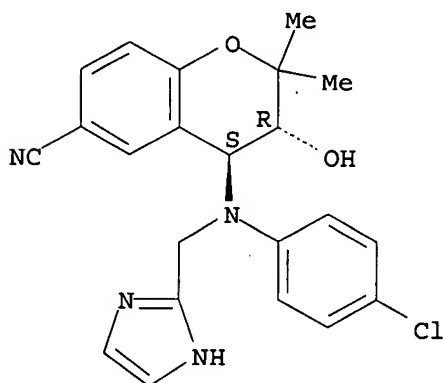
CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, phosphate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 166095-21-2

CMF C22 H21 Cl N4 O2

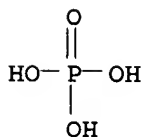
Absolute stereochemistry.



CM 2

CRN 7664-38-2

CMF H3 O4 P



RN 166096-01-1 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-dihydroxy-2,2-dimethyl-, (3R,4S)-, mononitrate (salt) (9CI) (CA INDEX NAME)

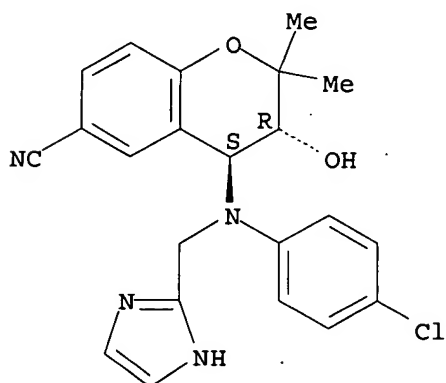
10523015.trn

CM 1

CRN 166095-21-2

CMF C22 H21 Cl N4 O2

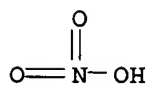
Absolute stereochemistry.



CM 2

CRN 7697-37-2

CMF H N O3



IT 166095-21-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

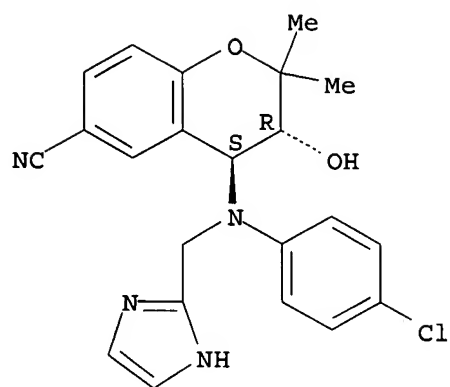
(preparation of 4-(arylamino)benzopyrans and related compds. as cardiovascular agents)

RN 166095-21-2 HCAPLUS

CN 2H-1-Benzopyran-6-carbonitrile, 4-[(4-chlorophenyl)(1H-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-, (3R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10523015.trn



=> log y

COST IN U.S. DOLLARS.

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

CA SUBSCRIBER PRICE

SINCE FILE	TOTAL
ENTRY	SESSION
115.80	462.01

SINCE FILE	TOTAL
ENTRY	SESSION
-15.60	-15.60

STN INTERNATIONAL LOGOFF AT 14:39:13 ON 20 APR 2007